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4- and 5-Acetamino Acetanthranils and Some Quinazolines Derived Therefrom.

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF PURE SCIENCE OF COLUMBIA UNIVERSITY.

BY

CARL GUSTAVE AMEND, B.S., M.A.

NEW YORK CITY

1910

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To my grandfather, Bernard G. Amend.

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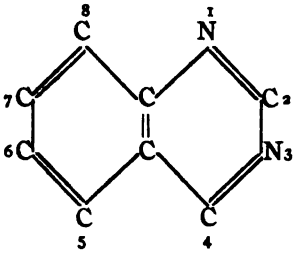
The investigations described in the following pages were undertaken at the suggestion of Professor Marston Taylor Bogert and carried out under his personal supervision. The author takes great pleasure in expressing his thanks, in this place, for the interest shown and advice received during the entire course of the work.

Carl G. Amend,
May, 1910.

Organic Chemistry Laboratory,
Havemeyer Hall, Columbia University.

HISTORY OF THE *bz*-AMINO-QUINAZOLINES.

Leaving out of consideration changes affecting the miazine nucleus, there are four possible *bz*-monoamino derivatives of the quinazolines; namely, the 5, 6, 7 and 8, as shown by the following structural formula:



Peter Griess[1] was the first to prepare a quinazoline of this kind. In the year 1869 Griess obtained a compound of m. p. 173° and to which he ascribed the formula $C_{10}H_{10}N_2O_3$ by passing cyanogen through a saturated alcoholic solution of anthranilic acid. This new compound when treated with hot hydrochloric acid gave a compound of the composition $C_8H_6N_2O_2$, which melted over 350° and which was later shown to be benzoylene urea (2,4-diketotetrahydroquinazoline or 2,4-dioxyquinazoline). Fuming nitric acid converted the latter product into a mononitro derivative, $C_8H_5(NO_2)N_2O_2$, and this on reduction with ammonium sulphide or tin and hydrochloric acid gave an amino compound which crystallized in light yellow needles, difficultly soluble in all neutral solvents, and which gave crystalline products with acids. To this base Griess ascribed the constitution $C_8H_5(NH_2)N_2O_2$ or $C_7H_4(NH_2)(CN)NO.HO$. Unfortunately, as the melting point of neither the nitro nor the amino compound is given, it is not known which of the four *bz*-aminoquinazolines of the 2,4-diketotetrahydro group he had thus obtained.

Dehoff,[2] 1890, obtained a mononitro derivative by treating anhydroacetyl-*o*-aminobenzamide (2-methyl-4-quinazolone) previously prepared by Weddige,[3] with fuming nitric acid of sp. gr. 1.5. He tried to reduce this nitro derivative with tin and hydrochloric acid, but failed to do so.

In the following year Thieme[4] obtained the same nitro derivative, prepared by Dehoff, by treating the ethyl ester of 5-nitro-*o*-acetaminobenzoic acid with alcoholic ammonia at 170° in a sealed tube. From this synthesis the position of the nitro group of Dehoff's nitro-quinazolone was established as that of 6. Thieme, however, does not mention any attempt at reducing his nitro product.

At about this time Zacharias,[5] upon treating in an analogous manner the ethyl ester of 3-nitro-*o*-acetaminobenzoic acid, prepared 8-nitro-2-methyl-4-quinazolone and also the dimethyl derivative. He reduced the former by treating it with tin or stannous chloride in hydrochloric acid solution. It crystallizes from water in colorless needles, melting at 230–2°. Zacharias could not completely separate the last traces of tin from his amino-quinazolone and therefore did not get good analytical figures. He tried other reducing agents but failed to get the desired result.

A *bz*-amino-quinazoline, but one which has besides a methyl group on a benzol nucleus, namely in position 7, was obtained by St. von Niementowski[6] in the year 1895. He obtained *m*-methyl-*o*-uraminobenzoyl (7-methyl-2,4-diketotetrahydroquinazoline) by condensing *o*-amino-*p*-toluylamide with chlorethylformate and subsequent splitting out of one molecule of alcohol. Nitration of this quinazoline gave a *bz*-mononitro derivative. This he reduced with tin and hydrochloric acid and recrystallized the resulting amino derivative from amyl alcohol. The amino-*m*-methyl-*o*-uraminobenzoyl melts at 308° and is almost entirely insoluble in water and in organic solvents. Niementowski also made a diamino derivative, which decomposes at 330°, from the corresponding dinitro compound obtained, besides the mono-nitro in the nitration of the starting product. The positions of the nitro, and therefore amino, groups in the benzol nucleus were not definitely determined either in the case of the mono- or di-derivatives.

Bogert and Chambers,[7] and Bogert and Seil,[8] prepared 5-nitro derivatives of 2-methyl-3-R-4-quinazolones and of 4-quinazolones, and in a later paper Bogert and Chambers,[9] 1906, mention the reduction of the nitro to the amino-quinazolones. This was accomplished by means of stannous chloride in hydrochloric acid solution. They thus prepared 5-amino-4-quinazolone, long, fine needles, carrying one molecule of water of crystallization and melting at 235–6° (cor.); also 5-amino-2-methyl-4-quinazolone, pale, reddish brown needles melting with decomposition at 295–310°. The latter product was obtained in very poor yield. It slowly darkens when exposed to light. Several derivatives of the former amino compound were likewise prepared.

In the year 1905 Bogert and Steiner[10] prepared 7-nitro derivatives from the 4-nitroacetanthranil. Bogert and Klaber[11] continued this work and prepared 7-amino-2-methyl-4-quinazolone by reducing the corresponding nitro compound with tin and hydrochloric acid and proceeding in the usual manner to obtain the free amine. This melts at 311° (cor.). When crystallized from water it carries one-half molecule of water of crystallization and, from alcohol, one-half molecule of alcohol of crystallization.

Up to this time all of the *bz*-amino-quinazolones had been obtained by the reduction of the corresponding nitro derivatives. Bogert and Chambers[12] succeeded in preparing these amino-quinazolones, *i. e.*, their acetyl derivatives, directly, without passing through the nitro stage, by starting with 2,4-diamino toluene, acetylating, oxidizing the diacetyl derivative to the corresponding acid, and obtaining 4-acetamino acetanthranil from this diacetylamino acid by treating with acetic anhydride. By the reaction of Anschütz, Schmidt, and Greiffenberg,[13] this anthranil can be converted into 7-acetamino-2-methyl-3-R-4-quinazolones by the action of primary amines. In this way they obtained 7-acetamino-2-methyl-4-quinazolone, not melting under 300°, and 7-acetamino-2,3-dimethyl-4-quinazolone melting at 272–3° (uncor.) by employing, respectively, ammonia and methylamine. The corresponding free amino-quinazolones resulted upon boiling these acetamino derivatives with a 10 per cent. solution of potassium hydroxide. The 7-amino-2-methyl formed fine white needles that darken on exposure to light and melt with a decomposition at 293–5°, and the 7-amino-dimethyl, needles, changing to short heavy prisms melting at 218–20° (uncor.).

Several 7-acetamino-2,6-dimethyl-3-R-4-quinazolones were obtained from the corresponding anthranil, namely, 4-acetamino-5-methyl-, by treating with primary amines, by Bogert and Kropff.[14] The above anthranil resulted on treating 4,6-diacetamino-*m*-toluic acid, a by-product in the oxidation of 4,6-diacetylamino-*m*-xylol to 4,6-diacetyl-amino isophthalic acid, with acetic anhydride. In this manner were made the 2,6-dimethyl- and the 2,6-dimethyl-3-phenyl-7-acetamino-4-quinazolones and also the free 7-amino-derivatives of the former.

The following is a list of the *bz*-monoamino-quinazolones described in the literature:

5-Amino Derivatives.

5-Amino-4-quinazolone (1 H_2O), m. p. 235–6°. Bogert and Chambers.

5-Amino-2-methyl-4-quinazolone, m. p. with decomposition 295–310°. Bogert and Chambers.

6-Amino Derivatives.

None have thus far been obtained.

7-Amino Derivatives.

7-Amino-2-methyl-4-quinazolone (½ H_2O or ½ alcohol), m. p. 311°. Bogert and Klaber.

7-Acetamino-2-methyl-4-quinazolone, m. p. not under 300°. Bogert and Chambers.

Free aminoquinazolone of the above (½ H_2O), m. p. with decomposition 293–5°. Bogert and Chambers.

7-Acetamino-2,3-dimethyl-4-quinazolone, m. p. 272–3° (uncor.). Bogert and Chambers.

Free aminoquinazolone of the above, m. p. 218–20° (uncor.). Bogert and Chambers.

7-Acetamino-2,6-dimethyl-4-quinazolone, m. p. about 330°. Bogert and Kropff.

Free aminoquinazolone of the above, m. p. not under 300°. Bogert and Kropff.

7-Acetamino-2,6-dimethyl-3-phenyl-4-quinazolone, m. p. 271° (uncor.). Bogert and Kropff.

8-Amino Derivatives.

8-Amino-2-methyl-4-quinazolone, m. p. 230–2°. Zacharias.

Besides these there are the quinazolones of Griess and St. von Niementowski where the position of the amino group on the benzol nucleus has not been determined.

GENERAL INTRODUCTION.

In the following work the synthesis of Bogert and Chambers[12] for the preparation of the 7-amino-, *i. e.*, acetamino-quinazolones has been employed; the general applicability of the reaction of Anschütz, Schmidt and Grieffenberg,[13] as applying to the action of primary amines on 4-acetamino acetanthranil, has been shown to hold good; a new series of *bz*-amino-quinazolones, *i. e.*, the 6-amino derivatives has been obtained; and, finally, the reactions of these *bz*-amino quinazolones have been investigated more fully than heretofore.

The 7-amino-, *i. e.*, acetamino-quinazolones were obtained, as previously mentioned, from 4-acetamino acetanthranil and this latter from 2,4-diamino toluene by acetylating, oxidizing, and treating the resulting 2,4-diacetaminobenzoic acid with acetic anhydride. By employing 2,5-diamino toluene, instead of the 2,4-, and treating in an analogous manner, a new anthranil, *viz.*, 5-acetamino acetanthranil was obtained. This, on treatment with primary amines yielded the 6-acetamino derivatives of the 2-methyl-3-R-4-quinazolones.

Due to the fact that we had available only a relatively small amount of the hydrochloride of the 2,5-diamino toluene, as compared with a large quantity of the crude 2,4-diamino toluene, and also that the oxidation of the diacetyl derivative of the former gave very much poorer results than in the case of the latter, most of the reactions were carried on with the 7-amino series.

2,4- and 2,5-Diaminobenzoic Acids.

Peter Griess,[15] 1872, obtained three isomeric nitro-aminobenzoic acids by boiling a mixture of dinitro-uraminobenzoic acids with water. Of these the α-nitro-amino acid gave, on reduction with tin and hydrochloric acid, an α-diaminobenzoic acid. Upon dry distillation this acid gave off carbon dioxide, yielding a compound of the composition $C_6H_8N_2$. This latter product agreed in its properties with the phenylene diamine described by Hofmann.[16] Griess had thus prepared the free 2,5-diaminobenzoic acid.

Two years later, Wurster[17] oxidized dinitrotoluol to dinitrobenzoic acid and reduced this product with tin and hydrochloric acid. This resulted in the formation of a tin double salt, which upon decomposition with hydrochloric acid gave small reddish crystals which he believed to be the hydrochloride of phenylene diamine, since he thought that carbon dioxide was split off simultaneously during the reduction process and that therefore the acid could not exist in the free state. To isolate the phenylenediamine Wurster distilled the hydrochloride with baryta. The diamine proved to be the meta. Thus Wurster's work tended to show that the 2,4-diaminobenzoic acid was incapable of existing in the free state.

V. Merz and W. Weith,[18] 1882, reduced a dinitrophthalic acid, of melting point 200°, with tin and hydrochloric acid and obtained thereby a *p*-diaminobenzoic acid. They could not get a melting point of this product as it became too dark upon heating. Distillation of this acid with soda lime gave *p*-phenylene diamine. The acid is thus the same one prepared by Griess.[15]

Kolbé,[19] in the year 1884, on heating nitroisatoic acid with tin and concentrated hydrochloric acid, got a liberation of hydrogen and carbon dioxide, obtaining a hydrochloric acid salt of a diaminobenzoic acid. He was unable to get the free diamino acid but thought that he had obtained the salt of the acid described by Griess[15] as α-diaminobenzoic acid.

C. Heussermann and H. Teichmann,[20] 1895, obtained reddish-brown, indistinct, crystals on reducing the ethyl ester of 2,5-dinitrobenzoic acid in alcoholic solution with tin and hydrochloric acid. They did not obtain the free acid itself.

Four years later Baeyer & Co.[21] patented the preparation of acetyl-*p*-phenylene-diamine carbonic acid, $C_6H_3(COOH)^1(NHCOCH_3)^3(NH_2)^6$, or, in other words, $C_6H_3(COOH)^1(NH_2)^2(NHCOCH_3)^5$ namely, 2-amino-5-acetamino-benzoic acid. In this patent they show that if *m*-acetaminobenzoic acid be nitrated in sulphuric acid solution with a calculated amount of nitric acid, a nitroacetamino acid results, which, on reduction, gives the acid mentioned above.

H. Seidel,[22] 1901, treated β-nitrophthalic acid with ammonia, getting thereby β-nitrophthalimide. This by means of the Hofmann reaction gave 2-isomeric nitroanthranilic acids, chiefly the meta ($COOH : NH_2 : NO_2 :: 1 : 2 : 4$), the other acid being the ($1 : 2 : 5$). By very careful reduction Seidel obtained the diamino acid in the case of the former. The latter gave on reduction, after acetylation, acetyl-*p*-phenylene diamine carbonic acid.

F. A. Pertsch,[23] in the following year, acetylated 5-nitro-2-anthranilic acid, getting thus 5-nitro-acetanthranilic acid and, by reduction of this nitro acid, 5-aminoacetylanthranilic acid ($COOH : NHCOCH_3 : NH_2 : 1 : 2 : 5$). We thus obtained the same acid as the one described by Seidel,[22] this being the isomer of the acid patented by Baeyer & Co.[21]

F. Ullmann and J. B. Uzbachian,[24] 1903, while working on the efficiency of permanganates as oxidizing agents, oxidized some 2,4-diacetamino toluol with calcium permanganate. By using 35.7 grams of this oxidizing agent they obtained a yield of 17 grams of acid from 20 grams of the acetylated diamine. 37.4 grams of potassium permanganate yielded only 12 grams of less pure acid even in the presence of a current of carbon dioxide. The melting point of the 2,4-diacetaminobenzoic acid is given as 261°. The acid forms white needles, readily soluble in hot, slightly in cold water and in glacial acetic acid, also readily soluble in hot alcohol; while it does not dissolve in benzol and ether even at the boiling point. These authors also prepared the free diamino acid by careful saponification of the above diacetyl derivative. This acid melts at about 140° and is unstable, gradually resinifying upon standing in contact with air.

Bogert and Kropff[14] obtained what they considered to be the ethyl ester of 2,4-diaminobenzoic acid. This was obtained as a by-product in the esterification of diacetylaminoisophthalic acid by the splitting off of one carbon dioxide. They were unable to obtain the acid itself, which they attempted to get by saponification of the ester with dilute potash solution.

Lucius and Brüning[25] have in this past year patented a method for obtaining 4-acetamino-2-aminobenzol-1-carbonic acid by oxidizing 2-nitro-4-acetamino toluol and subsequent reduction.

From the above review of the history of the 2,4- and 2,5-diaminobenzoic acids it can be seen that of the eight possibilities, namely; the free diamino acids, the 2-acetyl-4- or 5-amino, the 4- or 5-acetyl-2-amino, and the diacetylamino acids, all have been prepared with the exception of the 2-acetamino-4-aminobenzoic acid and the 2,5-diacetaminobenzoic acid. Incidental to the preparation of the 5-acetamino acetanthranil this last-named acid was obtained, resulting from the oxidation of the diacetyl derivative of 2,5-diamino toluene.

From the 2,4- and the 2,5-diacetamino benzoic acids the 4- and 5-acetamino acetanthranils were prepared, by treating with acetic anhydride, and from these the following quinazolones by the action of primary amines: 7-acetamino-2-methyl-3-R-4-quinazolones in which R is respectively, hydrogen, methyl, ethyl, normalpropyl, isoamyl, phenyl, α-naphthyl, p-phenetyl, p-anisyl, anilino, and amino; 6-acetamino-2-methyl-3-R-4-quinazolones in which R is respectively, hydrogen, methyl, ethyl, normalpropyl, phenyl, and amino; as well as some of the free amino derivatives.

In the case of 2°-butylamine the reaction did not go further than the amide stage, when this amine was made to act upon the 4-acetamino acetanthranil.

Almost all of the above quinazolones are crystalline products of high melting points. For the most part they are readily soluble in hot water and alcohol, while they do not dissolve in ether as a rule.

Those containing the grouping

$$—CO.NH— \rightleftarrows —C(OH):N—$$

in other words, those in which 3-R is replaced by hydrogen, are capable of acting both in the enolic and the ketonic form. The enolic condition is shown by their solubility in cold alkalies and the fact that they are precipitated from these solutions by saturation with carbon dioxide. While attempts to prove the keto group by condensation with phenylhydrazine failed, the fact that treatment with acylating reagents does not affect the 4-OH group showed that under these conditions the compounds reacted ketonic.

Treated with glacial formic acid the 7-amino-2-methyl-4 quinazolone gave a formyl derivative. The 6-amino when boiled with acetic anhydride was converted into the corresponding acetamino, while a similar treatment with propionic anhydride in the case of the 7-amino yielded a propionyl derivative. In all these cases a mono-acyl derivative was obtained, showing that the compound had always acted ketonic.

Both the 7- and the 6-free amino-quinazolones give a very mild isonitrile test of not unpleasant odor when boiled with chloroform and alcoholic potash solution.

A condensation with monochloracetic ester was attempted in the hope that a quinazolone derivative of indigo might be obtained, but no reaction would take place. Formaldehyde with potassium cyanide were then tried with a similar object in view but no definite reaction product could be isolated and as the reaction was very wasteful of material it had to be abandoned.

When treated with nitrous acid in the cold the 7-aminoquinazolone underwent diazotization, yielding dyes with various couplers. Upon boiling a freshly prepared diazo solution a strong evolution of nitrogen resulted, and from the solution thus obtained, a 7-oxyquinazolone was isolated.

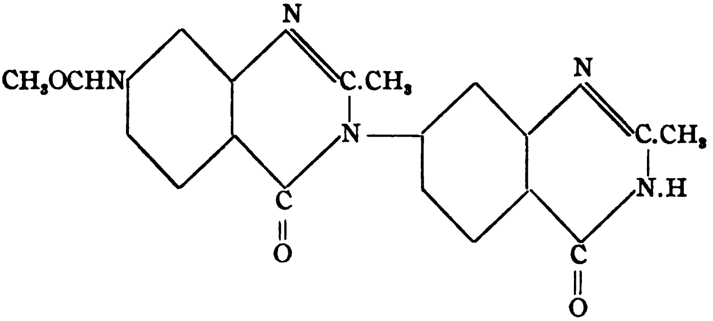
The NH_2 had thus been replaced by the OH group. Whereas this new *bz*-oxy-quinazolone showed no tendency to crystallize and was purified by dissolving in acid, reprecipitating with carbonate, and dissolving in alkali, reprecipitating with dilute acetic acid, upon acetylation it gave an acetyl derivative which crystallized readily from alcohol and gave good analytical figures.

A Sandmeyer reaction, by which it was hoped to replace the amino group by cyanogen, was also tried. A reaction took place but the yield of the product isolated from the reaction mixture was so poor that the attempt to obtain this result had to be abandoned.

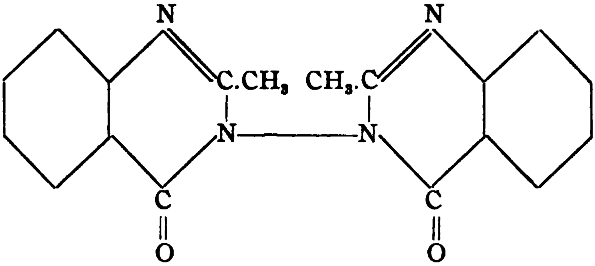
The 7-acetamino-2-methyl-4-quinazolone, when treated with a slight excess of fuming nitric acid at room temperature, gave a dinitro derivative. It was attempted to get a mononitro derivative by adding the quinazolone to concentrated sulphuric acid cooled to 0° C. and with the calculated quantity of potassium nitrate dissolved in it. Under these conditions no nitration took place, the unchanged product being recovered.

Bogert and Chambers[12] tried to obtain a brom derivative of 7-acetamino-2-methyl-4-quinazolone, but without a satisfactory result. By carefully adding bromine to the quinazolone, suspended in a hot solution of equal parts of glacial acetic acid and water, a vigorous reaction resulted, accompanied by the evolution of hydrobromic acid. A monobrom product was thus obtained. A large excess of bromine also yielded a monobrom derivative. To prove conclusively that the bromine had entered the nucleus, the above product was saponified with a 10 per cent. potassium hydroxide solution and the free amino derivative precipitated with carbon dioxide. In this manner a brom derivative of the corresponding 7-amino-quinazolone was obtained.

Since, in the case of the free *bz*-amino-quinazolones, we were dealing with primary amines we decided to ascertain whether a quinazolone of this type would condense with an anthranil, giving thus a quinazolone derivative, in position 3, of a quinazolone. Our attempt in this direction was crowned with success, the product resulting by the action of 7-amino-2-methyl-4-quinazolone upon 4-acetamino acetanthranil being represented by the following formula:



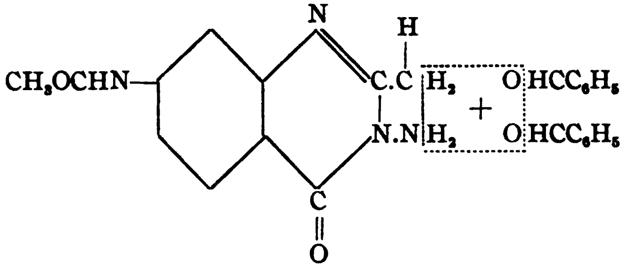
Diquinazolonyls have been obtained by treating hydrazine with twice the calculated quantity of an acetanthranil, the condensation taking place at both ends of the hydrazine, giving a product which can be represented as follows:



In the latter case the two quinazolone nuclei are united by an "N—N" union and the linkage is thus between the miazine rings. In our case we have secured a union of the benzol nucleus of the one quinazolone with the miazine of the other, the linkage being thus by means of a "C—N" union.

The condensation with hydrazine hydrate gave a quinazolone having the group N—NH_2. Compounds containing this group should condense with diacetosuccinic diethyl ester to form pyrrole derivatives according to Bülow[26] and Bülow and Weidlich.[27] Although several derivatives of this type have been obtained with quinazolones, 7-acetamino-2-methyl-3-amino-4-quinazolone refused to react.

Bülow[28] also showed that the N—NH_2 group reacted with benzaldehyde to form compounds of the benzylidene type. This reaction took place very readily in the case of the 3-aminoquinazolone referred to above, but the result was that not only did a benzylidene derivative form, but condensation of the benzaldehyde with the methyl group in position 2 also took place, giving thus a 2-styryl-3-benzalamino derivative as shown below:



This condensation product was always obtained when the 7-acetamino-2-methyl-3-amino-4-quinazolone was boiled for 5–10 minutes with an excess of benzaldehyde in an open vessel. The 6-acetamino derivative gave a similar result.

When this reaction was carried out with the 3,7-diamino-2-methyl-4-quinazolone a mixture of derivatives was obtained, by far the most abundant being the tribenzylidene product. Two dibenzylidene isomers were isolated besides, but due to the small amount obtained, it was not determined which of the three possible ones they were.

By the action of acetic anhydride on the 7-acetamino-2-methyl-3-amino-4-quinazolone a monoacetyl derivative of the 3-amino was obtained. In no case was the diacetyl derivative formed. This 3,7-diacetamino quinazolone reacts with benzaldehyde giving a monobenzylidene derivative, and since only the 2-methyl group can react the product is 3,7-diacetamino-2-styryl-4-quinazolone.

The work of Bogert and Gortner[29] on the condensation of benzaldehyde with 2-methyl-3-amino-4-quinazolone shows that condensation takes place on the amino group in position 3 before the methyl group is attacked. It was therefore of interest to us to determine whether the *bz*-amino would react more readily with benzaldehyde than the 2-methyl group or *vice versa*.

With this object in view, 7-amino-2-methyl-4-quinazolone was treated in an analogous manner, to that in which we had treated the 3-amino derivatives, with benzaldehyde. The first condensation product thus obtained gave a nitrogen content, on analysis, that corresponded to a monobenzylidene derivative. 7-Acetamino-2-methyl-4-quinazolone was then boiled with some benzaldehyde. In this case a monobenzylidene derivative was likewise obtained, and since only the methyl group in position 2 could have condensed in this latter reaction, the product formed must necessarily be 7-acetamino-2-styryl-4-quinazolone. It was therefore thought that by the action of acetic anhydride on the first product obtained, a compound analogous to the latter would result, or else no acetylation would take place. In either case the position of the benzylidene group would be determined. As we had run out of the first product in question, some more 7-amino-2-methyl-4-quinazolone was treated with benzaldehyde. This time a compound resulted which gave a nitrogen content just about half-way between the mono- and dibenzylidene condensation products. Another attempt gave a similar product, and still another, in which the quinazolone was boiled with a large excess of the aldehyde for half an hour in the hope of effecting a dibenzylidene condensation, resulted in the production of this same compound whose nitrogen content does not correspond either to a di- or a mono-condensation product. These latter compounds are capable of acetylation, showing that at least one of the hydrogens of the amino group is still free. Further than this we have been unable to throw any light upon the nature of this condensation.

Since the question, as to the relative ease of reaction of benzaldehyde upon the *bz*-amino or the 2-methyl group, had not been settled by the above attempt, the 7-amino-2,3-dimethyl-4-quinazolone was treated with benzaldehyde. In this case a definite monobenzylidene condensation resulted. The product obtained can be acetylated, giving a value of nitrogen corresponding to an acetylamino monobenzylidene derivative. The amino group has therefore not been attacked. There are, however, two methyl groups in the starting product. Work of Bogert and Beal, at present being carried on in this laboratory, has shown that the N-methyl group will not react with benzaldehyde. This leaves only the 2-methyl group in the above case capable of having reacted with this reagent. A condensation of 7-acetamino-2,3-dimethyl-4-quinazolone with benzaldehyde yielded a product identical with that obtained by acetylation of the condensation product of this reagent with the 7-amino-2,3-dimethylquinazolone above referred to.

It would thus seem from the above, as well as from condensations of 7-acetamino-2-methyl- and 3,7-diacetamino-2-methyl-4-quinazolones with benzaldehyde that the latter reacts readily with the 2-methyl group. Furthermore, that the *bz*-amino group has not a strong tendency to do so, the only case in which it is definitely shown to condense with benzaldehyde being that of 3,7-diamino-2-methyl-4-quinazolone, in which case the tribenzylidene derivative results.

EXPERIMENTAL.

The experimental work has been subdivided as follows:

I. Preparation of 4-acetamino acetanthranil and condensations of same with primary amines.

II. Preparation of 5-acetamino acetanthranil and condensations of same with primary amines.

III. Some properties and reactions of the *bz*-amino-quinazolones.*

IV. Action of benzaldehyde on some of the above quinazolones.

I. Preparation of 4-Acetamino Acetanthranil and Condensations of Same with Primary Amines.

2,4-Diamino toluene served as the starting product in the preparation of 4-acetamino acetanthranil. As mentioned in the introduction, we used the method of Bogert and Chambers.[12] The records of their results were, however, not at hand when this work was undertaken, but we have since received a complete copy of the same. In the first step of the synthesis, namely, the acetylation of the 2,4-diamino toluene, these authors slowly added the finely powdered diamine to a slight excess of acetic anhydride, diluted with an equal volume of glacial acetic acid. If the reaction did not begin at once the mixture was heated until it did. We added the whole amount of the finely powdered diamine, in one portion, to some undiluted acetic anhydride in the proportion of one part of the former to two of the latter. 10-gram portions were found most con-

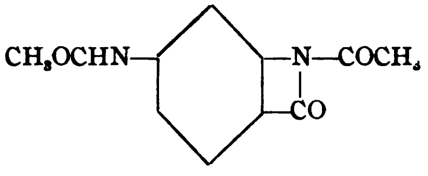
*The term "quinazolone" has been employed in all cases instead of 4-ketodihydroquinazoline.

venient to handle. A very vigorous reaction always resulted, accompanied by the liberation of much heat. When the reaction had somewhat abated the mass, which consisted of a rapidly thickening paste, was vigorously stirred to insure complete contact with the acetic anhydride. On cooling, the whole mass became solid. Carried out in this manner the reaction was ended in about one minute without requiring the application of any external heat. The product was then triturated in a mortar with cold water, filtered, washed with water, and finally boiled with the same to decompose the excess of anhydride, since in the subsequent oxidation, a neutral solution is required. When the pure 2,4-diamino toluene was used, clusters of long, snow-white, silky needles were obtained from the aqueous solution, melting at 220° (uncor.). Yield, 37.5 to 38.4 grams from 30 grams of starting product. For the main part of our work a crude 2,4-diamino toluene was employed. In this case the crystals obtained from the water were of a chocolate-brown color and the yield very much poorer. The product, however, did not require any further purification since, in the following oxidation, any impurities were eliminated and the acid obtained in as pure a state, but in much poorer yield, than in the case of the purer acetyl derivative.

The oxidation of the 2,4-diacetamino toluene to the diacetaminobenzoic acid was carried out as follows: Twenty grams of the acetyl product, together with 40 grams of magnesium sulphate, were added to about 2 liters of water in a large evaporating dish. To this solution, heated to boiling, were added in three portions at half-hour intervals, 40 grams of potassium permanganate. The mixture was vigorously agitated by means of a current of steam. The reaction was usually completed about 1 hr. after the addition of the last batch of permanganate, as seen by the disappearance of the pink color, taking thus from 2 to 2½ hrs. all told. The solution was then filtered hot to separate it from the precipitated manganese dioxide, the latter washed with boiling water, and the filtrate and washings concentrated to about 300–400 cc., and allowed to cool. About half a gram of the unchanged diacetyl derivative crystallized out at this point when the pure starting product was employed. This was filtered off and the filtrate then acidified with hydrochloric acid. After a few seconds the 2,4-diacetaminobenzoic acid was precipitated in a microcrystalline form. The acid thus obtained is salmon-colored, due to traces of manganese. It melted with decomposition at 261° (cor.), after one crystallization from alcohol, from which solvent it comes down in fine white needles. For our purposes it was not necessary to purify the acid. The yield from the pure diacetamino toluene is 17.6 to 19.9 grams of acid (unpurified) from 20 grams of starting product. In the case of the crude diamine only 15–16 grams of acid resulted from the oxidation of 20 grams and 2–3, instead of ½ gram above cited, of the unchanged product was recovered.

The object of the magnesium sulphate in the above oxidation is to keep the solution neutral.[30] This method seems to give just as satisfactory results as that of Ullmann and Uzbachian[24] given in the introduction.

4-Acetamino Acetanthranil,



Bogert and Chambers[12] prepared this anthranil, but did not analyze it. They give a melting point of 216° (uncor.).

In obtaining the anthranil we heated 20–25 grams of acetic anhydride to boiling and then added the well-dried and finely powdered acid. It was found most advisable to add the acid in small portions to the boiling anhydride, stirring after each addition, thus enabling the solution to remain fairly clear throughout the whole operation. In this manner much troublesome bumping can be avoided. After the addition of the last of the acid, the solution was boiled for 2–3 minutes longer and was then allowed to cool. Upon cooling the whole mass gradually solidified, crystallizing in rosettes of light yellow needles. Yield, 8+ grams of anthranil from 10 grams of acid.

For purposes of analysis the anthranil was recrystallized several times from acetic anhydride. White needles were obtained, melting at 220° (cor.).

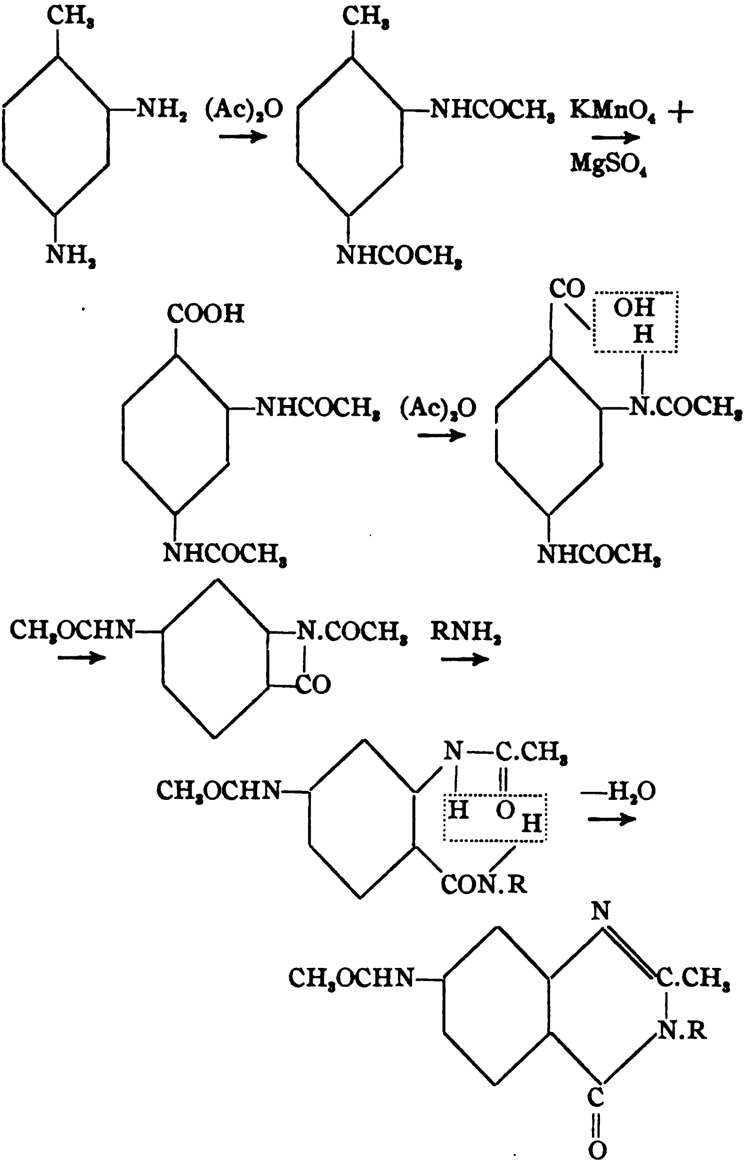
A nitrogen analysis of the product gave the following result:

0.1077 gram of sample gave 12.2 cc. of nitrogen at 21° and 768 mm.

	Calculated for $C_{11}H_{10}O_3N_2$. Per cent.	Found. Per cent.
N	12.90	13.04

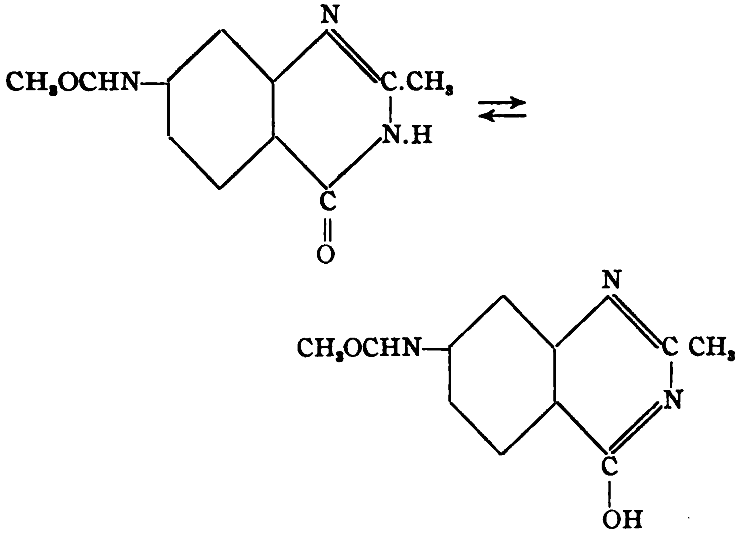
The pure product is slightly tribo-electric. It decomposes when exposed to moist air, giving back the acid from which it was obtained. Solvents containing moisture effect the same result.

This anthranil, when treated with primary amines, gives quinazolones, amides being the intermediate stage in the reaction. The synthesis of the anthranil, as well as the formation of quinazolones therefrom, can be illustrated graphically as follows:


CH₃
NH₂
NH₂
(Ac)₂O
CH₃
NHCOCH₃
NHCOCH₃
KMnO₄ +
MgSO₄
COOH
NHCOCH₃
NHCOCH₃
(Ac)₂O
CO
OH
H
N.COCH₃
NHCOCH₃
CH₃OCHN
N.COCH₃
CO
RNH₂
CH₃OCHN
N—C.CH₃
H O H
CON.R
—H₂O
CH₃OCHN
N
C.CH₃
N.R
C
O

7-ACETAMINO-2-METHYL-4-QUINAZOLONE

(*7-Acetamino-2-methyl-4-oxyquinazoline*),



This quinazolone was prepared by Bogert and Chambers[12] by treating the 4-acetamino acetanthranil with an excess of ammonium hydroxide solution, boiling the solution, usually with the addition of a little alkali, and precipitating the quinazolone by passing carbon dioxide into the alkaline solution. They found that it formed fine white crystals that do not change color in the air; that it did not melt under 300° C., at which point it darkened somewhat; that it is soluble in boiling water or alcohol, slightly so in ethyl acetate, insoluble in ether, carbon tetrachloride, and toluene, soluble in hydrochloric acid with evolution of heat; and that it contains water of crystallization when crystallized from water. An analysis calculated to the dry basis gave 19.1 per cent. nitrogen, the theory being 19.35.

We did not find it necessary to use alkali in any case, heating alone being sufficient to effect the transformation from the amide to the quinazolone stage. It thus comes out of the original solution in short, fine needles. These recrystallized from alcohol gave the following figures:

0.1501 gram of sample gave 26.4 cc. of nitrogen at 24° and 753 mm.

	Calculated for $C_{11}H_{11}O_2N_3$. Per cent.	Found. Per cent.
N	19.35	19.53

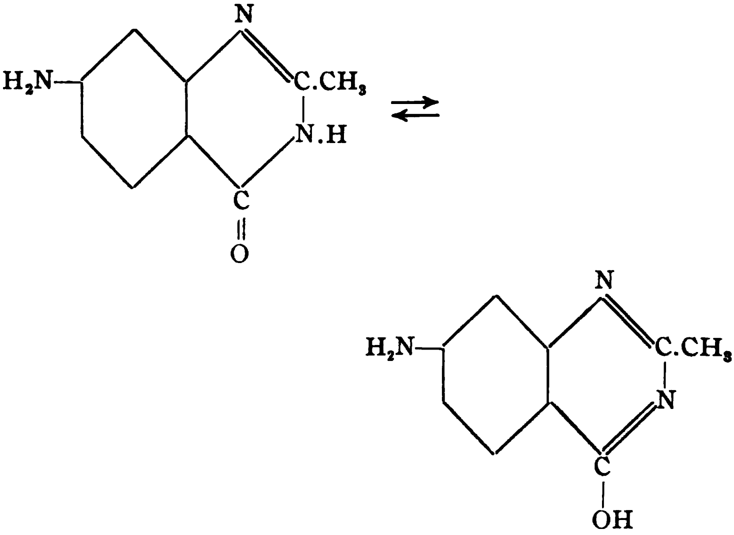
Crystallized from water: 1.0363 grams of air-dried sample lost 0.15 gram on drying to constant weight at 100–10° C.

	Calculated for $C_{11}H_{11}O_2N_3.2H_2O$. Per cent.	Found. Per cent.
H_2O	14.23	14.46

The purified product softens around 342° and melts at 344° (cor.).

7-AMINO-2-METHYL-4-QUINAZOLONE

(*7-Amino-2-methyl-4-oxyquinazoline*),



The same authors prepared this quinazolone by boiling the above acetamino derivative with a dilute solution of potassium hydroxide for about an hour and then saturating this solution with carbon dioxide. They claim that it melts with decomposition at 293–5°; that it forms fine white needles that darken on exposure to light; and that its solubilities are similar to those of the preceding compound. Crystallized from water it carries one-half molecule of water of crystallization, as shown by the following analysis:

Theory for $^1/_2$ H_2O, 4.9%. Found, 4.8%.

Calculated to the dry basis an ultimate analysis gave:

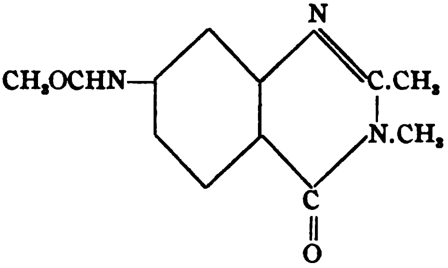
	Theory. Per cent.	Found. Per cent.
C	61.7	61.8
H	5.1	5.2

They also prepared the hydrochloride by adding strong hydrochloric acid to the quinazolone or to its solution in ethyl acetate. This formed a light brown, granular powder that decomposed on heating. The chlorplatinate was obtained by adding a warm solution of platinum chloride to a warm solution of the above hydrochloride, this resulting in the formation of red, granular, crystals.

	Calculated for $(C_9H_{10}ON_3)_2PtCl_6$. Per cent.	Found. Per cent.
Pt	25.6	25.6

As mentioned in the introduction, Bogert and Klaber[11] also obtained this quinazolone by reduction of the corresponding 7-nitro compound. They give a melting point of 311° (cor.) which agrees with that found by us for this compound.

7-Acetamino-2,3-dimethyl-4-quinazolone,



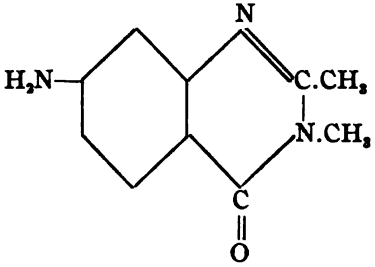
This was likewise prepared by Bogert and Chambers[12] by boiling the 4-acetamino acetanthranil with a 30 per cent. solution of methylamine, with the addition of a little alkali. They give the following properties for the product obtained: fine white needles of melting point 273° (uncor.); soluble in hot water or alcohol, slightly so in acetone, insoluble in ether, ligroin and carbon tetrachloride. No analysis was made of the product. We again found the addition of alkali unnecessary to the quinazolone formation and therefore just boiled the anthranil with the diluted methyl amine solution. This caused the solution of the anthranil and, upon cooling, the separation of the quinazolone as white silky needles. The product was then recrystallized from alcohol, a Dumas nitrogen analysis giving the following result:

0.1139 gram of sample gave 18.7 cc. of nitrogen at 23° and 760 mm.

	Calculated for $C_{12}H_{13}O_2N_3$. Per cent.	Found. Per cent.
N	18.2	18.5

The purified quinazolone gave a melting point of 284° (cor.).

7-Amino-2,3-dimethyl-4-quinazolone,



In an analogous manner to that in which the 7-amino-2-methyl-4-quinazolone was obtained, Bogert and Chambers[12] prepared the above compound. There is this difference, however, that in the case of the dimethyl compound it is not necessary to precipitate with carbon dioxide after hydrolysis, since the product is insoluble in the cold alkaline solution, not being capable of acting in the enolic condition. Bogert and Chambers noted the fact that if this solution be slowly cooled or if allowed to stand in a warm place for some time the fine needles, which are a result of rapid cooling, change to short, heavy prisms. They darken on exposure to air and melt at 218–20° (uncor.). We, likewise, obtained a mixture of needles and prisms upon cooling of the alkaline solution.

Bogert and Chambers also claim that this product contains water of crystallization. It appeared to us that this might be the case. The quinazolone, however, when dried in a vacuum desiccator, over sulphuric acid, gave a nitrogen content which showed that no water was present. If, therefore, the compound contains water of crystallization it loses it readily.

0.1003 gram of sample gave 19.6 cc. of nitrogen at 20.5° and 762 mm.

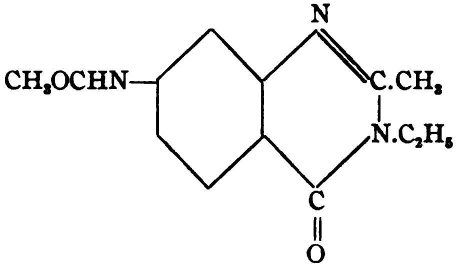
	Calculated for $C_{10}H_{11}ON_3$. Per cent.	Found. Per cent.
N	22.22	22.36

The quinazolone is readily soluble in warm water, alcohol, and benzol; slightly soluble in chloroform; insoluble in ether and ligroin. It unites with hydrochloric acid with evolution of heat and melts at 224° (cor.)

The same authors prepared the chlorplatinate of the above by adding a warm solution of the hydrochloride to a warm solution of platinum chloride. Red crystals were obtained which gave the following results for platinum:

	Calculated for $(C_{10}H_{12}ON_3)_2PtCl_6$. Per cent.	Found. Per cent.
Pt	24.7	24.6

7-Acetamino-2-methyl-3-ethyl-4-quinazolone,



Upon heating a mixture of 4-acetamino acetanthranil with a dilute solution of ethylamine, solution resulted and, after cooling, glistening pearly plates were precipitated. These were recrystallized from alcohol, from which solvent the quinazolone comes down in short, white needles. The following result for the nitrogen content was obtained:

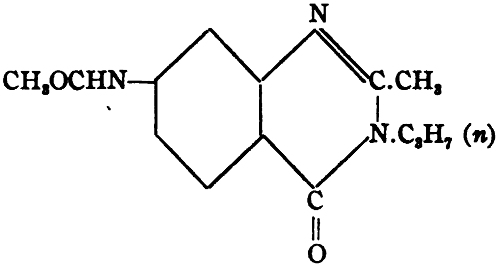
0.202 gram of sample gave 30.8 cc. of nitrogen at 22° and 751 mm.

	Calculated for $C_{13}H_{15}O_2N_3$. Per cent.	Found. Per cent.
N	17.14	17.07

The quinazolone, after purification, melts at 254° (cor.). It is slightly soluble in cold and very, in warm, alcohol.

From hot water it comes down on cooling in clusters of long, fine, white, silky needles.

7-Acetamino-2-methyl-3-n-propyl-4-quinazolone,

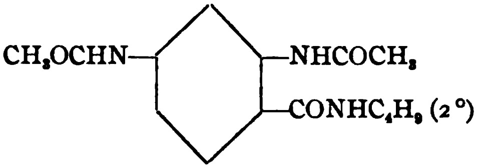


The anthranil was boiled in an analogous manner with *n*-propylamine, care being taken not to have the solution of the amine too dilute. Upon cooling, the quinazolone was precipitated in white, silky needles. It was recrystallized from water, from which it comes down in rosettes of similar needles. This product is more readily soluble in cold alcohol than the 3-ethyl quinazolone. It melts at 206–7° (cor.).

0.129 gram of sample gave 19 cc. of nitrogen at 24° and 758 mm.

	Calculated for $C_{14}H_{17}O_2N_3$. Per cent.	Found. Per cent.
N	16.22	16.46

2,4-Diacetamino-2°-butylbenzamide,



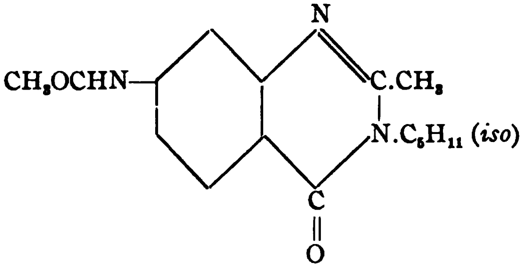
When the anthranil was added to a diluted solution of 2°-butylamine it went into solution on heating, but nothing separated out when this solution was allowed to cool. Again heating the solution, this time with the addition of a little alkali, did not cause the desired result. The anthranil was then heated with the pure solution of the amine, which resulted n the precipitation of needles on cooling. When this solution was diluted and boiled, again no product would separate out upon cooling. The reaction was therefore carried out with the pure solution of the amine. The needles above referred to were filtered off and recrystallized several times from dilute alcohol, from which solvent short, white needles are obtained. The well-dried crystals were then analyzed, a Dumas nitrogen determination giving the following results:

0.1213 gram of sample gave 15.4 cc. of nitrogen at 19° and 761 mm.

	Calculated for (quinazolone) $C_{15}H_{19}O_2N_3$. Per cent.	Calculated for (amide) $C_{15}H_{21}O_3N_3$. Per cent.	Found. Per cent.
N	15.38	14.43	14.61

It is evident from the above figures that the quinazolone was not obtained, the reaction going no further than the amide stage. The product was dried at 100–20° for analysis and could therefore not have contained any water of crystallization. This amide melts at 235° (cor.). It is soluble in hot water, very readily soluble in hot, and fairly so in cold alcohol.

7-Acetamino-2-methyl-3-isoamyl-4-quinazolone,



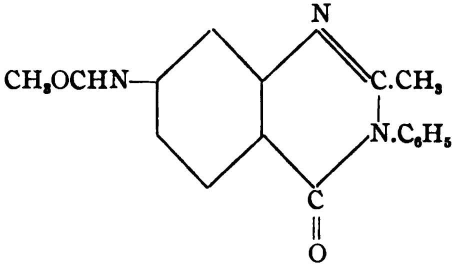
With isoamylamine peculiar results were also obtained. No condensation took place with the anthranil when boiled with a dilute solution of this amine, either in the absence or presence of alkali. Furthermore, nothing separated out on cooling a heated solution of an excess of the pure amine with the anthranil, as was the case with the 2°-butylamine. Upon diluting this latter solution with water and boiling, a white, flaky, precipitate resulted after several hours' standing. Four recrystallizations from dilute alcohol removed all traces of impurities, the resulting product being pure white and giving the following nitrogen content upon analysis:

0.12 gram of sample gave 15.8 cc. of nitrogen at 24° and 760 mm.

	Calculated for $C_{16}H_{21}O_2N_3$. Per cent.	Found. Per cent.
N	14.63	14.76

The quinazolone was therefore obtained in this case. It is insoluble in cold water, fairly soluble in cold alcohol and hot water; while it dissolves very readily in hot alcohol. The melting point is 288° (cor.).

7-Acetamino-2-methyl-3-phenyl-4-quinazolone,



Some 4-acetamino acetanthranil was thoroughly mixed in a small beaker with a slight excess of aniline. The mixture was then heated on an oil bath with constant stirring.

A brown, brittle, resinous substance resulted upon cooling. This ground to a light brown powder soluble in hot alcohol, from which solvent it comes down in minute, white, pearly octahedrons.

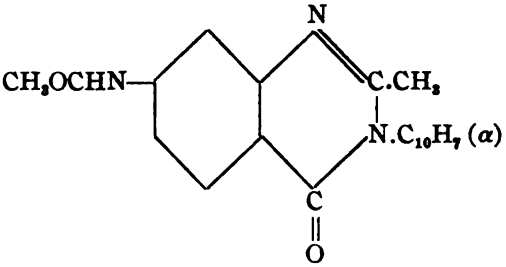
A Dumas nitrogen gave the following results:

0.1782 gram of sample gave 22.4 cc. of nitrogen at 22.5° and 768 mm.

	Calculated for $C_{17}H_{15}O_2N_3$. Per cent.	Found. Per cent.
N	14.33	14.24

The melting point of the pure quinazolone is 276° (cor.). It is insoluble in hot or cold ether, chloroform, acetone, and water; very slightly soluble in hot carbon tetrachloride; and dissolves readily in hot alcohol and nitrobenzol.

7-Acetamino-2-methyl-3-α-naphthyl-4-quinazolone,

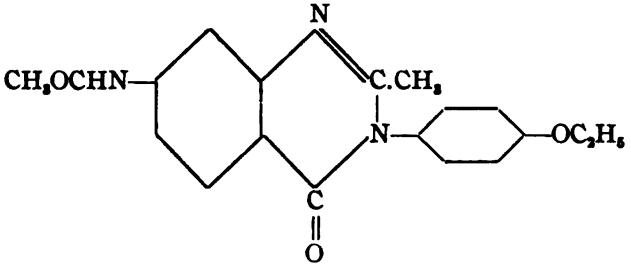


This quinazolone was obtained by a direct fusion of α-naphthylamine and 4-acetamino acetanthranil in molecular proportions. A brittle, very tribo-electric mass was thus obtained. It is soluble in hot and cold methyl and ethyl alcohols and is precipitated from these solutions by the addition of water in an amorphous condition, not crystallizing under any conditions. Glacial acetic acid dissolves it, but upon diluting this solution an amorphous mass is likewise obtained. Several other solvents were tried, but the product refused to crystallize from any of them. It was finally obtained fairly pure by treating the mass, ground to a fine powder, with chloroform. An oil was first formed; this went into solution, and finally was reprecipitated as fine flakes, the precipitation being aided by heating. These flakes were filtered off, washed with ether, in which they are insoluble, and then dried. The final product is a gray powder melting at 256° (cor.). This gave the following nitrogen content:

0.1166 gram of sample gave 12.3 cc. of nitrogen at 23° and 770 mm.

	Calculated for $C_{21}H_{17}O_2N_3$. Per cent.	Found. Per cent.
N	12.24	12.05

7-Acetamino-2-methyl-3-p-phenetyl-4-quinazolone,



It was first attempted to effect a condensation by boiling an alcoholic solution of *p*-phenetidine with the anthranil. No reaction took place, however, not even with the addition of alkali. The two constituents were then fused together in molecular proportions, on an oil bath. The cool fusion was very readily soluble in warm alcohol. From dilute alcohol clusters of short, slightly pink needles were obtained. After two recrystallizations the substance gave the following analytical figures:

0.1987 gram of sample gave 22 cc. of nitrogen at 20° and 760 mm.

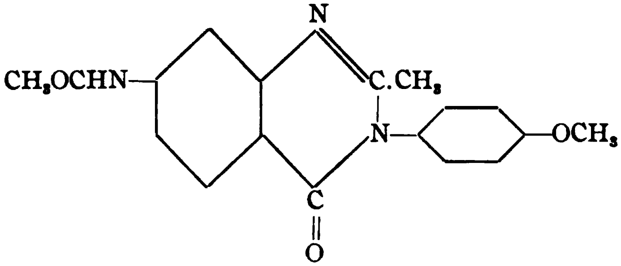
0.0998 gram of sample gave 0.2470 gram of carbon dioxide and 0.0528 gram of water.

	Calculated for $C_{19}H_{19}O_3N_3$. Per cent.	Found. Per cent.
C	67.66	67.50
H	5.64	5.88
N	12.46	12.66

This quinazolone is interesting inasmuch as it resembles phenacetine, having the acetamino group para to the ethoxy group in the entire molecule, and differing from the latter in possessing an additional quinazolone nucleus. Its physiological properties have, however, not been investigated.

The pure product melts at 259° (cor.). It is insoluble in ether, difficultly soluble in hot water and carbon tetrachloride, while it dissolves in boiling benzol and very readily in warm chloroform, ethyl, and isoamyl alcohols.

7-Acetamino-2-methyl-3-p-anisyl-4-quinazolone,



By using *p*-anisidine instead of *p*-phenetidine the above quinazolone resulted. The fusion was carried on in the same manner as in the previous case, molecular proportions of the two constituents being employed. A salmon-colored melt resulted. Upon several recrystallizations from dilute alcohol, flesh-colored, glistening, octahedrons, melting at 273° (cor.), were obtained.

A nitrogen analysis of the product thus purified gave the following result:

0.1029 gram of sample gave 11.7 cc. of nitrogen at 19° and 768 mm.

	Calculated for $C_{18}H_{17}O_3N_3$. Per cent.	Found. Per cent.
N	13.0	13.2

The purified product is insoluble in hot and cold ether, chloroform, and water. It dissolves slowly in boiling acetone and very readily in warm nitrobenzol, ethyl and isoamyl alcohols.

A condensation with *p*-amino-benzonitril was next tried, the nitrile being fused with the anthranil in molecular proportions of 1 : 1. From the cooled melt, which did not resolidify while hot, although heated to 140°, rosettes of slightly yellowish-white needles were obtained upon crystallizing from dilute alcohol. These were recrystallized until a pure white product resulted, melting with decomposition at 258° (cor.).

A nitrogen analysis gave a value that is very much too low for the calculated per cent. of nitrogen, assuming the formation of the quinazolone, as shown below:

0.1003 gram of sample gave 11.6 cc. of nitrogen at 18° and 760 mm.

	Calculated for $C_{18}H_{14}O_2N_4$. Per cent.	Found. Per cent.
N	17.61	13.36

The result obtained figured out just right for six molecules of water of crystallization. The product was therefore heated for three hours at 130–60° C. and again analyzed. This time:

0.1003 gram of sample gave 12.1 cc. of nitrogen at 25° and 758 mm.

	Found. Per cent.
N	13.41

The discrepancy does therefore not seem to be due to any water of crystallization.

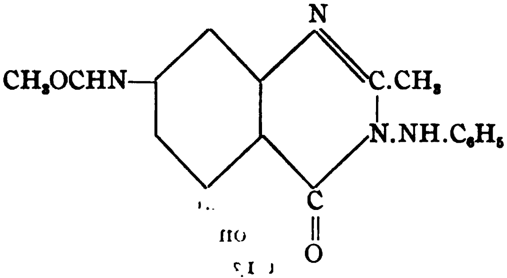
Upon repeating the fusion, heating this time to a still higher temperature (170°), the mass again remained liquid, *i. e.*, did not resolidify until cooled. This portion gave a slightly lower melting point and the following nitrogen content:

0.1214 gram of sample gave 13.8 cc. of nitrogen at 23° and 769 mm.

	Found. Per cent.
N	12.96

Some action other than the formation of the quinazolone, therefore, seems to take place. We have been unable to ascertain the nature of the product formed beyond the fact that it seems to give an amino acid upon saponification, judging by a copious evolution of ammonia, and the solubility of the product resulting, on boiling this compound with a 10 per cent. potassium hydroxide solution.

7-Acetamino-2-methyl-3-anilino-4-quinazolone,



No reaction took place when a slight excess of phenylhydrazine was added to some of the anthranil in the cold. Upon gently warming the mixture, the anthranil went into solution and an extremely vigorous action resulted. The solution, which was at first of a light yellow color, quickly changed to a dark red, accompanied by very violent boiling, even upon immediate withdrawal of the source of external heat. We were unable to isolate any product from this mixture, deep-seated decomposition undoubtedly taking place. Furthermore, the application of heat could not be so regulated as to cause a moderate reaction. Some of the phenylhydrazine was then diluted with many times its volume of alcohol and to this solution was added the anthranil. This time the reaction was very moderate upon warming. The yellow liquid first formed upon solution of the anthranil gradually changed color, becoming finally dark red. After boiling for half an hour, in a small flask with a reflux condenser attached, the excessive alcohol was evaporated off and the concentrated solution allowed to cool. Yellow nodules, consisting of clusters of fine white needles, were thus obtained. These were recrystallized several times from alcohol, white, feathery needles resulting.

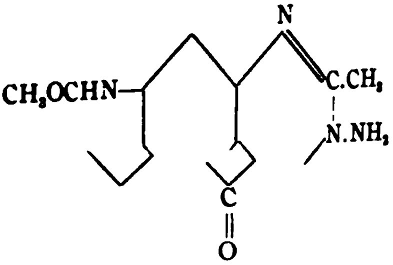
The following nitrogen value was obtained:

0.1006 gram of sample gave 16.2 cc. of nitrogen at 23.5° and 773 mm.

	Calculated for $C_{17}H_{16}O_2N_4$. Per cent.	Found. Per cent.
N	18.2	18.4

This quinazolone is soluble in hot water and in most of the usual organic solvents. Thus it is somewhat soluble in hot ether, soluble in benzol, hot and cold chloroform and acetone, hot alcohol, and very much so in warm nitrobenzol and isoamyl alcohol. It does not dissolve readily in boiling carbon tetrachloride. Upon heating in a capillary tube, it softens at 208° and melts to a clear liquid at 214° (cor.).

7-Acetamino-2-methyl-3-amino-4-quinazolone,



When the anthranil was added to a moderately strong solution of hydrazine hydrate it remained in suspension for a few seconds, heat was developed, and finally a snow-white, pasty mass was precipitated. This was then diluted with water and the solution boiled for several minutes. The product first formed was thus converted into fine glistening needles of a slight cream color. Recrystallized from a fairly large volume of 95 per cent. alcohol and dried at about 100° C. these gave a nitrogen value about 1 per cent. too low. The compound was then dried to constant weight in the air-bath at 125–30°. (Heating at 110° was not sufficient to drive out all the water of crystallization.)

0.5174 gram of sample lost 0.0378 gram.

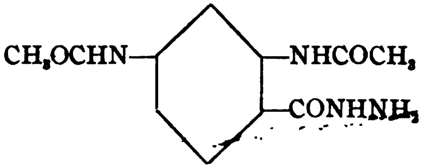
	Calculated for $C_{11}H_{12}O_2N_4.H_2O$. Per cent.	Found. Per cent.
H_2O	7.20	7.31

A Dumas nitrogen on 0.1017 gram of the dried substance gave 21.4 cc. of nitrogen at 19.5° and 768 mm.

	Calculated for $C_{11}H_{12}O_2N_4$. Per cent.	Found. Per cent.
N	24.14	24.38

The pure product melts sharply at 268° (cor.). It is insoluble in ether, benzol, cold alcohol, and water; difficultly soluble in hot chloroform; dissolves in a fairly large volume of hot alcohol and water; and is very readily soluble in warm nitrobenzol. When a current of dry hydrochloric acid gas was passed through a suspension of this quinazolone in ether, heat was developed, and a hydrochloride obtained. This gave a nitrogen value corresponding to 1½ molecules of hydrochloric acid to 1 of quinazolone. The hydrochloride melts with violent decomposition at 312° (cor.), darkening before melting.

2,4-Diacetamino-benzhydrazide,



Some of the white, pasty mass, obtained in the first stage of the above reaction, was separated from the main reaction mixture. Upon closer examination it was found to consist of very fine, short needles. These were recrystallized several times from alcohol, dried at 80° and analyzed.

0.1025 gram of sample gave 20.2 cc. of nitrogen at 25° and 775 mm.

	Calculated for $C_{11}H_{14}O_3N_4$. Per cent.	Found. Per cent.
N	22.4	22.43

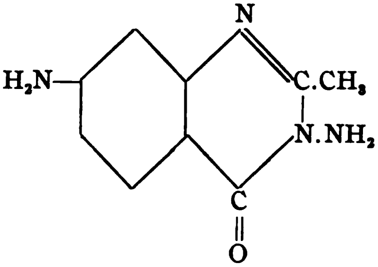
The compound was then heated in the air-bath for 6 hrs. at 120–40° to determine whether it would lose any water of crystallization, as the quinazolone had done. No loss of weight was evident and the nitrogen content of the dried product likewise showed that the quinazolone had not resulted by this treatment.

0.1025 gram of sample gave 20.7 cc. of nitrogen at 24° and 757 mm.

	Found. Per cent.
N	22.55

It would seem from these figures that the product thus isolated is the intermediate hydrazide. It gave the same melting point as the quinazolone which may, however, be due to the fact that at higher temperatures it is converted into the latter by the action of heat.

3,7-Diamino-2-methyl-4-quinazolone,



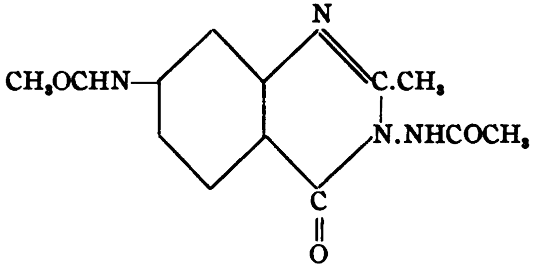
This quinazolone resulted on boiling the corresponding 7-acetamino derivative with 10 per cent. potassium hydroxide solution for about half an hour. Upon cooling of this solution clusters of white, silky needles separated out, the whole mass finally solidifying. This was diluted with water, filtered, washed thoroughly to get rid of the excess of alkali, and then recrystallized from dilute alcohol. The free diamino quinazolone melts at 238° (cor.).

A Dumas nitrogen determination obtained the following figures:

0.1011 gram of sample gave 26.2 cc. of nitrogen at 22.5° and 770 mm.

	Calculated for $C_9H_{10}ON_4$. Per cent.	Found. Per cent.
N	29.5	29.7

3,7-Diacetamino-2-methyl-4-quinazolone,



When the 7-acetamino-3-aminoquinazolone was boiled with an excess of acetic anhydride it went into solution readily, no noticeable reaction, however, taking place previous to the application of heat. Upon continued boiling the acetyl derivative was precipitated in the hot solution as minute, white tufts of needles. At this point the heating was discontinued and the remainder of the product allowed to crystallize out. The crystals were then filtered off, washed with alcohol, dried, and analyzed without purification, the object of the last step being to determine whether the mono-, the di-, or a mixture of the two acetyl derivatives of the 3-amino group had been obtained. The crude product melted at 301° (cor.) and gave the following result for nitrogen:

0.1136 gram of sample gave 20 cc. of nitrogen at 18.5° and 762 mm.

	Calculated for $C_{13}H_{14}O_3N_4$. Per cent.	Found. Per cent.
N	20.44	20.34

It would thus seem that the acetylation resulted in the formation of a monoacetyl derivative only. Subsequent acetylations confirmed this result, a diacetyl product never being obtained. The product was purified by recrystallization from alcohol, giving the following nitrogen content:

0.1212 gram of sample gave 21.5 cc. of nitrogen at 22.5° and 775 mm.

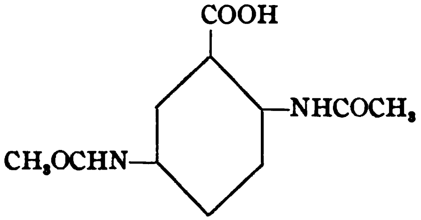
	Found. Per cent.
N	20.44

The melting point of the purified product is 304° (cor.). It is readily soluble in hot alcohol and water, coming down from the latter solvent in feathery needles that carry water of crystallization. From hot alcohol it is precipitated on cooling in a micro-crystalline state.

II. Preparation of 5-Acetamino Acetanthranil and Condensations of Same with Primary Amines.

For the preparation of 5-acetamino acetanthranil the hydrochloride of 2,5-diamino toluene served as starting product. On account of the presence of this hydrochloric acid, fused sodium acetate had to be used, together with acetic anhydride, in the first step of the synthesis, namely, the acetylation. The large amount of salt thus introduced retarded the reaction, only a small amount of heat being developed when the hydrochloride was added in the cold to a mixture of the anhydride and sodium acetate. The reaction was therefore carried on as follows: Twenty grams of acetic anhydride, to which the calculated amount (4.2 grams) of fused sodium acetate had been added, were heated in a small beaker to boiling. To this hot solution were added 10 grams of the finely powdered diamine hydrochloride. The diamine went into solution, a fairly vigorous reaction taking place. The mixture was then boiled for a few minutes and allowed to cool. This resulted in the formation of a brown paste which was triturated with water, white flakes being thus obtained. These upon recrystallization from water gave small, white plates melting at 214° (uncor.). Yield, about 14 grams from 20 grams of starting product.

2,5-Diacetaminobenzoic Acid,



This acid was prepared in an essentially analogous manner to that used in obtaining its 2,4-isomer. In this case the oxidation tends largely either to completely burn up the substance or to leave it unchanged. Thus from a 10-gram portion of the starting product, 3 grams of the unchanged diacetyl derivative were recovered and only 2 grams of the acid resulted.

It was at first thought that the low results in the yield of acid might be due to the fact that the latter is somewhat volatile with steam since, as mentioned in the preparation of the 2,4-acid, a vigorous current of steam was employed to keep the solution well agitated. The next oxidation was therefore carried on in a large flask with a reflux condenser attached. In this case, with similar quantities used, 3.7 grams of starting material were recovered, the same amount of acid being formed. By using 30 grams of permanganate for 10 of the diacetyl compound, which is just twice the amount of the former required by the theory, 4 grams of acid resulted. The acid does not seem to be volatile with steam, the yield depending therefore rather upon the amount of permanganate used. This result was borne out by subsequent oxidations in the open dish, using a current of steam. The larger the amount of the oxidizing agent employed, however, the smaller that of the unchanged product recovered, that is, the more the substance is completely broken up.

When finally the filtrate from the unchanged product was acidified with hydrochloric acid no immediate precipitation occurred, the acid forming slowly and coming down micro-crystalline. The 2,5-diacetaminobenzoic acid is of salmon color and cannot be obtained white by merely crystallizing from alcohol, bone-blacking from this solvent being required to accomplish this result. It melts with decomposition at 262° (cor.).

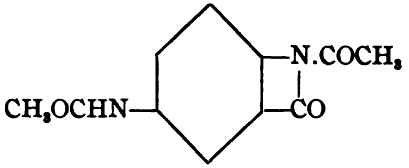
A Dumas nitrogen determination gave the following figures:

0.1701 gram of sample gave 17.8 cc. of nitrogen at 20° and 760 mm.

	Calculated for $C_{11}H_{12}O_4N_2$. Per cent.	Found. Per cent.
N	11.86	11.97

The pure acid is soluble in hot nitrobenzol, aniline, alcohol, in strong mineral acids, alkalies, and carbonates; it is insoluble in dilute hydrochloric and acetic acids, hot and cold ether, carbon tetrachloride, benzol, and ligroin.

5-Acetamino Acetanthranil,



By adding the above acid in small portions to boiling acetic anhydride in the proportion of 1 part of the former to 2 of the latter and boiling a few minutes after the last addition, large dark yellowish brown needles of 5-acetamino acetanthranil are precipitated on cooling. Yield, 3½ grams from 5 grams of acid. The anthranil was recrystallized several times from acetic anhydride for analytical purposes, clusters of coarse, yellowish brown needles resulting.

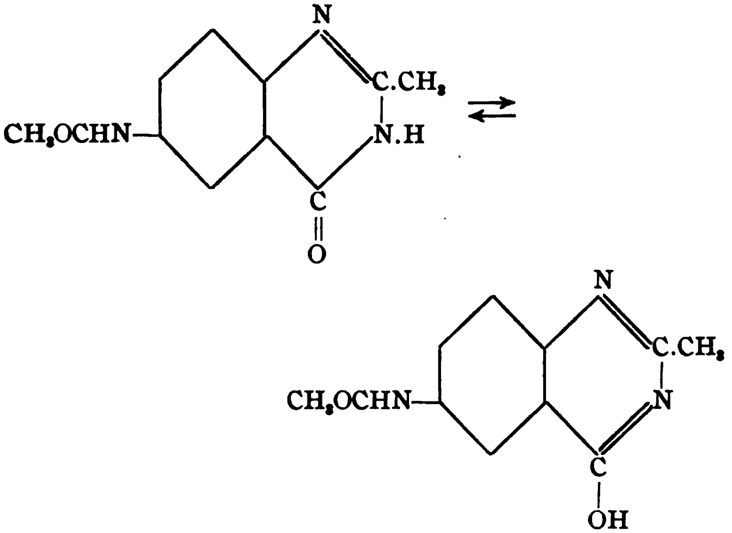
0.216 gram of sample gave 25.8 cc. of nitrogen at 26° and 749 mm.

	Calculated for $C_{11}H_{10}O_3N_2$. Per cent.	Found. Per cent.
N	12.90	13.02

The pure anthranil melts at 253° (cor.). It is unstable in the presence of moisture, by which it is converted into 2,5-diacetaminobenzoic acid.

6-ACETAMINO-2-METHYL-4-QUINAZOLONE

(*6-Acetamino-2-methyl-4-oxyquinazoline*),



Upon heating this anthranil with a dilute solution of ammonia it went into solution and, upon cooling, the above quinazolone was precipitated in minute crystals. From alcohol this can be obtained in small, coarse needles. The purified product gave a melting point of 350° (cor.) and the following nitrogen:

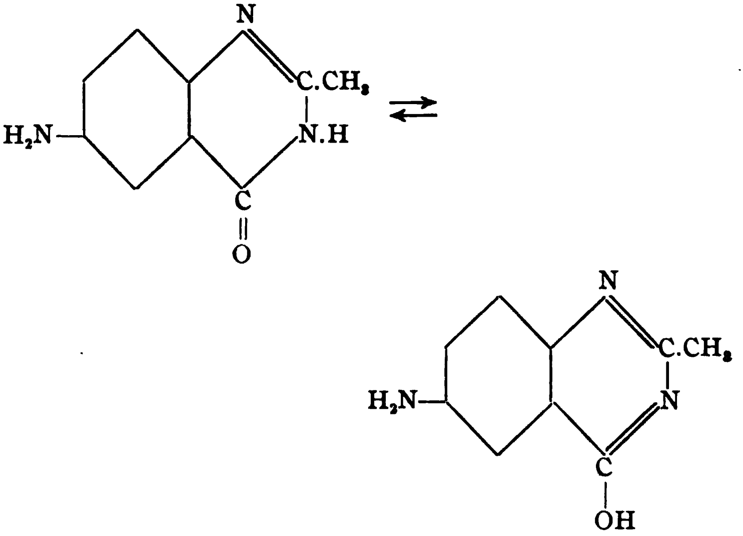
0.152 gram of sample gave 25.8 cc. of nitrogen at 21° and 760 mm.

	Calculated for $C_{11}H_{11}O_2N_3$. Per cent.	Found. Per cent.
N	19.35	19.33

In general properties it resembles its 7-isomer.

6-AMINO-2-METHYL-4-QUINAZOLONE

(*6-Amino-2-methyl-4-oxyquinazoline*),



Just as in the case of the 7-acetamino-quinazolone, when the above-described quinazolone is boiled with 10 per cent. potassium hydroxide solution, and the latter saturated with carbon dioxide after cooling, the free amino product results. It is precipitated from the alkaline solution as short, white, silky needles. The filtrate shows a bluish fluorescence which becomes quite pronounced upon standing for several days. From water rosettes of long, white needles are obtained, highly refractive towards light. These completely lose their lustre upon heating in an air-bath to 70–80°.

A Dumas nitrogen upon the purified substance gave the following figures:

0.1003 gram of sample gave 21.4 cc. of nitrogen at 22° and 752 mm.

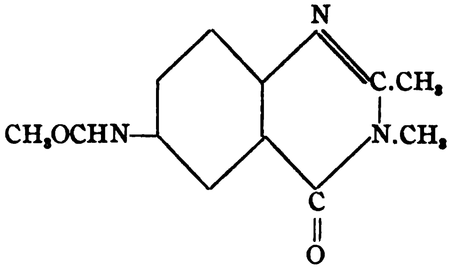
	Calculated for $C_9H_9ON_3$. Per cent.	Found. Per cent.
N	24.00	23.92

Upon exposure to light the product darkens somewhat. If heated in a capillary tube it darkens around 300°, melts around the edges at 304°, becoming very dark brown, and finally completely melting at 314–5° (cor.).

Bogert and Geiger[31] have succeeded recently in obtaining this amino-quinazolone by reducing with tin and hydrochloric acid the nitro-quinazolone described by Dehoff.[2] The melting point that they obtain for their amino product agrees with the one above given. A mixture of their product with ours melted sharply at 314° (cor.). Furthermore, upon acetylation, a product resulted which agreed in its melting point with the 6-acetamino-2-methyl-4-quinazolone described above, while a mixture of the two acetyl derivatives melted at 349° (cor.). The products are therefore identical.

Besides displaying the usual solubilities due to its enolic condition, the 6-amino-quinazolone is insoluble in hot and cold ether and ligroin; very slightly soluble in hot chloroform and benzol; soluble in hot alcohol and hot acetone. It dissolves very readily in warm nitrobenzol, ethyl, and isoamyl alcohols.

6-Acetamino-2,3-dimethyl-4-quinazolone,



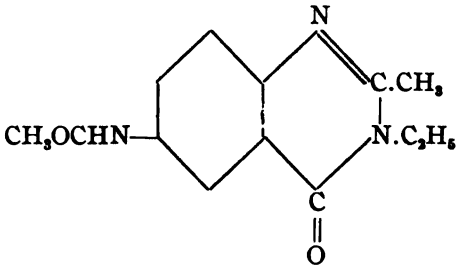
The above quinazolone resulted on heating the anthranil with some dilute methylamine. The former went into solution and the dimethyl quinazolone was precipitated in the boiling solution as white, silky needles. It was recrystallized from alcohol for analysis. In this solvent the product is slightly soluble in the cold, and very readily in the hot solution. It is also soluble in boiling water and does not dissolve in cold water or ether. The melting point of the pure product is 278° (cor.).

A Dumas nitrogen gave the following result:

0.1012 gram of sample gave 16.1 cc. of nitrogen at 22° and 768 mm.

	Calculated for $C_{12}H_{13}O_2N_3$. Per cent.	Found. Per cent.
N	18.18	18.22

6-Acetamino-2-methyl-3-ethyl-4-quinazolone,

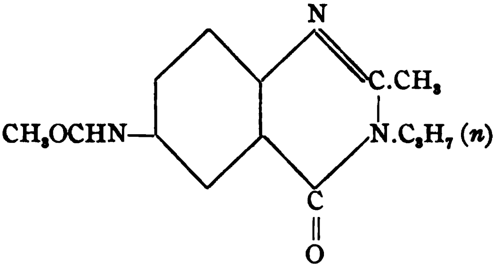


When the 5-acetamino acetanthranil was boiled with a dilute solution of ethyl amine, it went into solution, but no product separated out on cooling. The addition of a few drops of alkali to the boiling solution produced no noticeable result, when the latter was allowed to cool. However, after about 24 hours of standing, clusters of long, white, silky needles separated out. These when recrystallized from water gave a nitrogen content which corresponds to that calculated for the quinazolone, and a melting point of 229° (cor.).

0.106 gram of sample gave 16.6 cc. of nitrogen at 27° and 766 mm.

	Calculated for $C_{13}H_{15}O_2N_3$. Per cent.	Found. Per cent.
N	17.14	17.43

6-Acetamino-2-methyl-3-n-propyl-4-quinazolone,



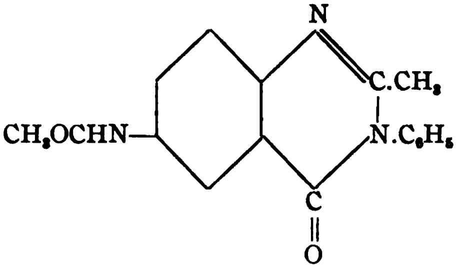
In the case of *n*-propylamine alkali was also found to be necessary to bring about the formation of the quinazolone. The latter is quite soluble even in cold alcohol, and was therefore recrystallized from water. Long, white, silky needles were obtained, melting at 181° (cor.).

A Dumas nitrogen determination gave the following figures:

0.1001 gram of sample gave 14.4 cc. of nitrogen at 25.5° and 769 mm.

	Calculated for $C_{14}H_{17}O_2N_3$. Per cent.	Found. Per cent.
N	16.22	16.45

6-Acetamino-2-methyl-3-phenyl-4-quinazolone,

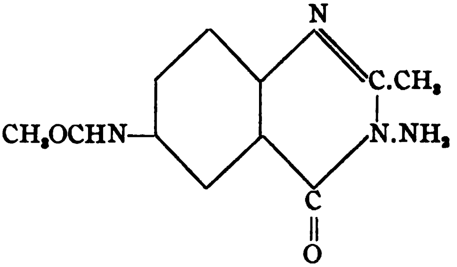


This quinazolone resulted by a direct fusion of the anthranil with a slight excess of aniline. The fused mass was rather difficultly soluble in boiling water and somewhat soluble in cold alcohol. It was therefore recrystallized from dilute alcohol, from which solvent small, brown plates were precipitated on cooling. These melt at 255° (cor.) and gave a nitrogen content which agreed with that calculated for the quinazolone.

0.1114 gram of sample gave 14.5 cc. of nitrogen at 25° and 756 mm.

	Calculated for $C_{17}H_{15}O_2N_3$. Per cent.	Found. Per cent.
N	14.33	14.43

6-Acetamino-2-methyl-3-amino-4-quinazolone,



A dilute solution of hydrazine hydrate reacted readily with this anthranil. The latter went into solution when boiled with an excess of this reagent, and upon cooling the quinazolone precipitated in rosettes of white, silky needles, the whole mass finally solidifying. It is very soluble in hot, and insoluble in cold water. Recrystallized from alcohol it gave a melting point of 264° (cor.), and the following nitrogen value:

0.0996 gram of sample gave 21 cc. of nitrogen at 18° and 758 mm.

	Calculated for $C_{11}H_{12}O_2N_4$. Per cent.	Found. Per cent.
N	24.14	24.29

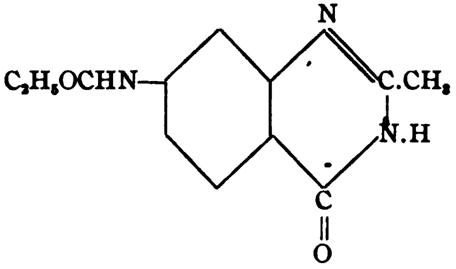
The above condensations were thought to be sufficient to demonstrate the general applicability of the action of primary amines on 5-acetaminoacetanthranil, resulting in the formation of 6-*bz*-amino-quinazolones therefrom.

III. Some Properties and Reactions of the bz-*Amino-quinazolones.*

Upon boiling the 7-amino-2-methyl-4-quinazolone with chloroform and alcoholic potash solution a very mild isonitrile test, of not unpleasant odor, was obtained. The corresponding 6-amino derivative gave a similar result.

In an attempt to prove the keto group by the formation of the hydrazone, the former quinazolone was treated with phenylhydrazine. No condensation took place either in alcoholic solution in the presence of acetic acid or when the two constituents were directly fused together. We were therefore unable to obtain a direct proof of the keto group. By the following reaction, however, we obtained an indirect proof:

7-Propionylamino-2-methyl-4-quinazolone,



Upon heating the 7-amino-2-methyl-4-quinazolone with an excess of propionic anhydride a thin paste was first formed and then the whole mass solidified. The reaction product was boiled with water to decompose the excess of anhydride. It went into solution and was reprecipitated on cooling in clusters of white, silky needles. These were recrystallized again from water, requiring a much larger amount to dissolve it than the original free amino-quinazolone does. The product thus purified melted at 326° (cor.). A crystallization from alcohol gave a melting point of 326–7° (cor.). In both cases the compound begins to soften at about 317°.

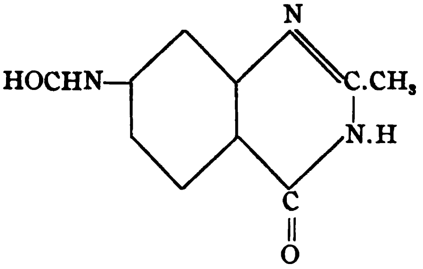
A Dumas nitrogen determination on 0.1111 gram of sample gave 18.6 cc. of nitrogen at 26° and 756 mm.

	Calculated for $C_{12}H_{13}O_2N_3$. Per cent.	Found. Per cent.
N	18.18	18.48

The dried propionyl derivative is tribo-electric. It is fairly soluble in hot water in the presence of dilute organic acids, but requires a considerably larger amount of pure water to dissolve it. In alcohol it is more insoluble than the free amino-quinazolone. From this solvent it comes down in exceedingly short needles.

If the quinazolone had acted in the enolic condition in the above reaction the 4-OH group would have been acylated and a dipropionyl derivative would have resulted.

7-Formylamino-2-methyl-4-quinazolone,



The 7-amino-2-methyl-4-quinazolone was boiled for four hours with glacial formic acid, using a reflux condenser, and the excess of acid then evaporated off. The solution was diluted with water and neutralized with sodium carbonate. The precipitate thus obtained was filtered off, washed with water, and recrystallized from the latter. Clusters of feathery needles were thus obtained. The purified product gave rise to the following figures:

0.1037 gram of sample gave 18.6 cc. of nitrogen at 21° and 761 mm.

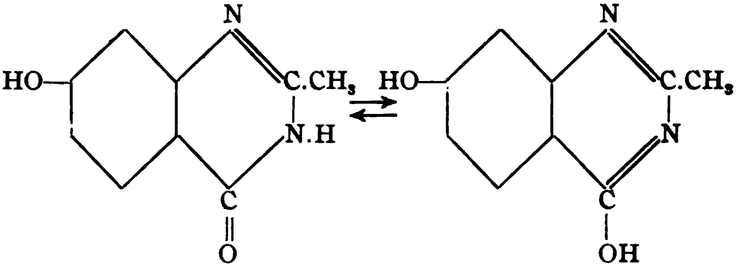
	Calculated for $C_{10}H_9O_2N_3$. Per cent.	Found. Per cent.
N	20.69	20.46

The formyl derivative darkens, upon heating, around 300°, becoming darker with increased temperature, and melting completely at about 339° (cor.), to a brown liquid. It did not give a test with the fuchsin aldehyde reagent, but gave a silver mirror, after several days' standing, when added to an ammoniacal silver nitrate solution in the presence of sodium hydroxide.

A condensation of the 7-amino-2-methyl-4-quinazolone was next attempted with monochloracetic ester in order that by subsequent treatment a quinazolone derivative of indigo might be obtained. Under no conditions tried would this condensation take place, the unchanged quinazolone being always recovered as shown by a melting point and a nitrogen determination.

With a similar object in view, the same quinazolone was boiled with potassium cyanide and formaldehyde in aqueous solution. No definite product could be isolated from this reaction mixture and as the reaction was very wasteful of starting material, it was not further investigated.

7-Oxy-2-methyl-4-quinazolone (4,7-dioxy-2-methyl-quinazoline),



When the hydrochloric acid solution of 7-amino-2-methyl-4-quinazolone was treated with nitrous acid in the cold, it underwent diazotization and dyes could be obtained with this solution by the action of various couplers. If, however, the diazo solution was diluted with water and heated, a vigorous evolution of nitrogen took place, resulting in the replacement of the amino by the hydroxy group. The reaction was carried on as follows:

An aqueous solution of 0.69 gram of sodium nitrite was slowly added to a solution of 1.75 grams of the hydrochloride of the amino-quinazolone, with constant stirring, the solution being well cooled. At the completion of the reaction, the mixture was diluted to about 200 cc. with water, giving a yellow solution. Upon heating this, a strong evolution of nitrogen resulted before the boiling point was reached. The solution was boiled until no more gas was given off. At the end of the reaction it was of a strong orange color and upon neutralization with sodium carbonate, after cooling, a voluminous yellow precipitate was obtained. This could not be crystallized from any of the usual solvents and was therefore purified by dissolving and reprecipitating with acid and carbonate, and alkali and dilute acetic acid. Upon treating with fairly strong hydrochloric acid the greater part readily dissolved, leaving a small amount of dark orange, insoluble portion. This latter product may have been formed by the action of nitrous acid on the imide group producing thus a nitrosamine derivative. Too small an amount resulted to investigate further than that it dissolved readily in alkali, yielding an intensely red solution, and that hydrochloric acid reprecipitated it in the form of a gelatinous, orange-colored precipitate which could not be filtered. The oxy-quinazolone was reprecipitated from the original hydrochloric acid solution by adding sodium carbonate until just neutral, a light brown precipitate resulting. This was again dissolved in hydrochloric acid, filtered from a very slight insoluble portion, and again precipitated with carbonate. It was then dissolved in alkali, yielding a red solution, and reprecipitated with dilute acetic acid, since it would not do so by saturating with carbon dioxide. The product thus purified does not melt below 345° (cor.), at which point it begins to darken.

A Dumas nitrogen analysis gave the following figures:

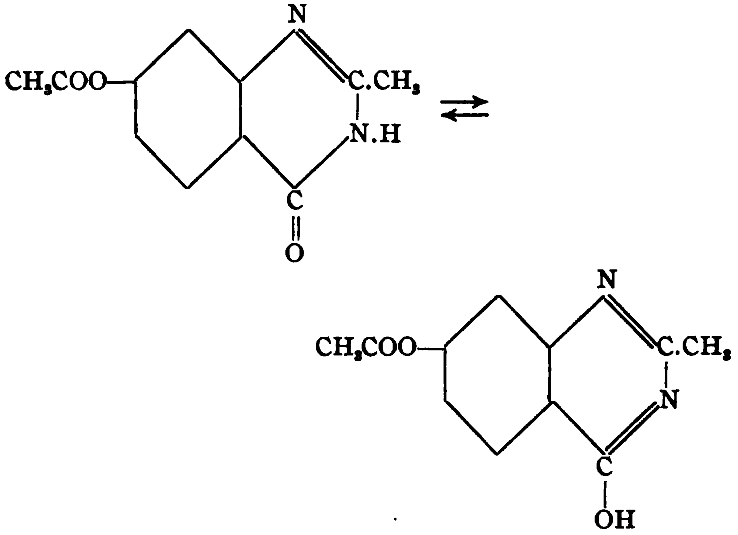
0.1499 gram of sample gave 21.8 cc. of nitrogen at 23° and 755 mm.

	Calculated for $C_9H_8O_2N_2$. Per cent.	Found. Per cent.
N	15.91	16.28

This oxy-quinazolone, or dioxy-quinazoline, is more acid than the amino-quinazolone from which it is obtained, as shown by the fact that it will not precipitate when carbon dioxide is passed into its alkaline solution. It is insoluble in ether, chloroform, carbon tetrachloride, benzol, toluene, and acetone; while it dissolves readily in hot ethyl and isoamyl alcohols, aniline, and nitrobenzol.

7-ACETOXY-2-METHYL-4-QUINAZOLONE

(*7-Acetoxy-2-methyl-4-oxy-quinazoline*),



Since the 7-oxy-quinazolone above described could not be crystallized, it was determined to acetylate it and try to purify its acetyl derivative. The compound was therefore boiled with acetic anhydride for one hour, using a reflux condenser. Fairly long boiling was required to effect solution, which, when obtained, was of a reddish brown color. Upon addition of sodium carbonate to the cooled and diluted reaction mixture a light brown, very finely divided product resulted. This, after filtering and washing, to free of salts formed, could be recrystallized from alcohol. It comes down from this solvent in large, light brown needles. These soften at about 262° and melt at

266° (cor.). The following figures were obtained for this acetyl derivative.

0.1116 gram of sample gave 13 cc. of nitrogen at 22° and 752 mm.

0.1517 gram of sample gave 0.3367 gram of carbon dioxide.

0.1532 gram of sample gave 0.0666 gram of water.

	Calculated for $C_{11}H_{10}O_3N_2$. Per cent.	Found. Per cent.
C	60.55	60.53
H	4.60	4.83
N	12.84	13.06

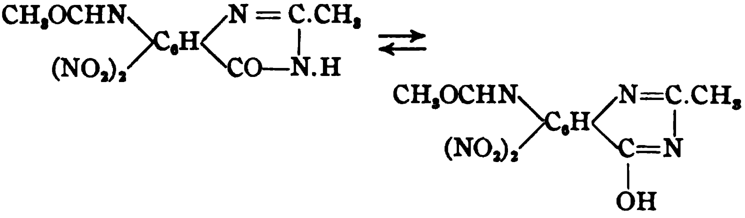
An attempt to replace the amino group by cyanogen by means of the Sandmeyer reaction did not prove as successful as the hydroxy replacement. A reaction took place, but no product could be distilled over with steam from the resulting mixture. A substance was finally extracted with carbon tetrachloride, using a Soxhlet extractor. After this solution had been evaporated to dryness the resulting white, crystalline mass was recrystallized from alcohol two times. Feathery needles were obtained melting at 303–4° (cor.). The nitrogen result on this product is too low and since only 0.1 gram of product resulted from 5 grams of starting material, the reaction was not repeated.

0.0998 gram of sample gave 18.8 cc. of nitrogen at 20.5° and 777 mm.

	Calculated for $C_{10}H_7ON_3$. Per cent.	Found. Per cent.
N	22.6	22.0

DINITRO-7-ACETAMINO-2-METHYL-4-QUINAZOLONE

(Dinitro-7-acetamino-2-methyl-4-oxy-quinazoline),



When the 7-acetamino-2-methyl-4-quinazolone was added to a small amount of fuming nitric acid at room temperature, it went into solution with a hissing noise, accompanied by the development of heat, and followed by the separation of yellow to orange nodules upon cooling. This mixture was then largely diluted with water and the solution boiled. The nodules went into solution and carbon dioxide was evolved, the amount of the latter depending upon that of acid used at the start. A dark orange product separated out this time when the solution was allowed to cool. This product was recrystallized several times from dilute acetic acid, from which solvent it comes down as orange granules. Upon heating, this nitro derivative begins to decompose at 295°, the decomposition continuing to 305°, when a black melt is obtained. The product dissolves in alkali, giving a dark orange color and reprecipitating from this solution slowly by saturation with carbon dioxide, more readily with dilute acetic acid.

A nitrogen determination gave a value corresponding to a dinitro derivative. The positions of the nitro groups have not been determined, but, judging by the usual orientation in such cases, they are most likely 6 and 8.

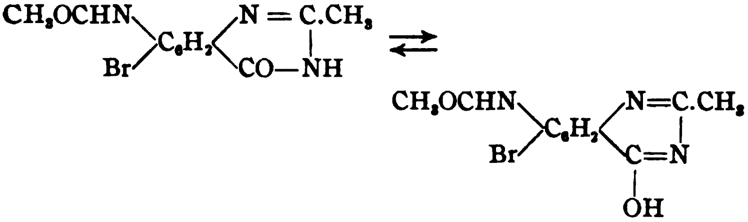
0.0979 gram of sample gave 19.7 cc. of nitrogen at 20.5° and 758 mm.

	Calculated for (mono-) $C_{11}H_{10}O_4N_4$.	Calculated for (di-) $C_{11}H_9O_6N_5$.	Found.
N	21.38	22.8	22.9

An attempt was then made to obtain a mononitro derivative by nitrating in sulphuric acid solution at 0° with the calculated quantity of potassium nitrate, but no nitration took place, as shown by a melting point and a nitrogen determination.

BROM-7-ACETAMINO-2-METHYL-4-QUINAZOLONE

(*Brom-7-acetamino-2-methyl-4-oxy-quinazoline*),



Upon adding bromine to a suspension of the 7-acetaminoquinazolone in a hot solution of equal parts of glacial acetic acid and water, a very vigorous reaction ensued. The quinazolone went into solution accompanied by the evolution of hydrobromic acid and bromination products of acetic acid. The bromine derivative thus formed then precipitated in the hot solution as minute needles. The mixture was allowed to cool, diluted with water, and filtered. After a thorough washing with water, the product was recrystallized from a large volume of alcohol with the addition of some glacial acetic acid to aid solution. It is thus obtained in clouds of exceedingly fine, cream-colored needles. These begin to darken at about 287° and melt with decomposition at 292° (cor.). The compound gave the following results for nitrogen and bromine:

0.1186 gram of sample gave 14.6 cc. of nitrogen at 18° and 753 mm.

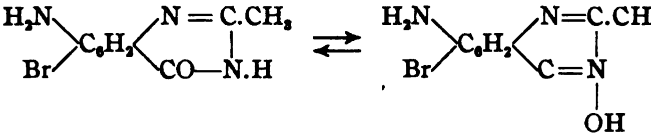
0.1104 gram of sample gave 0.072 gram of silver bromide.

	Calculated for $C_{11}H_{10}O_2N_3Br$. Per cent.	Calculated for $C_{11}H_9O_2N_3Br_2$. Per cent.	Found. Per cent.
N	14.2	11.2	14.1
Br	27.03	42.66	27.75

The pure product is very difficultly soluble in boiling alcohol. It can be recrystallized from dilute acetic acid, while it does not dissolve in either hot or cold water.

The action of a large excess of bromine was then tried, under similar conditions to the above. The crude product obtained in this case was orange-colored, due to impurities. These could be washed out by macerating with cold alcohol and the same monobrom derivative resulted upon purification.

Brom-7-amino-2-methyl-4-quinazolone (Brom-7-amino-2-methyl-4-oxy-quinazoline),



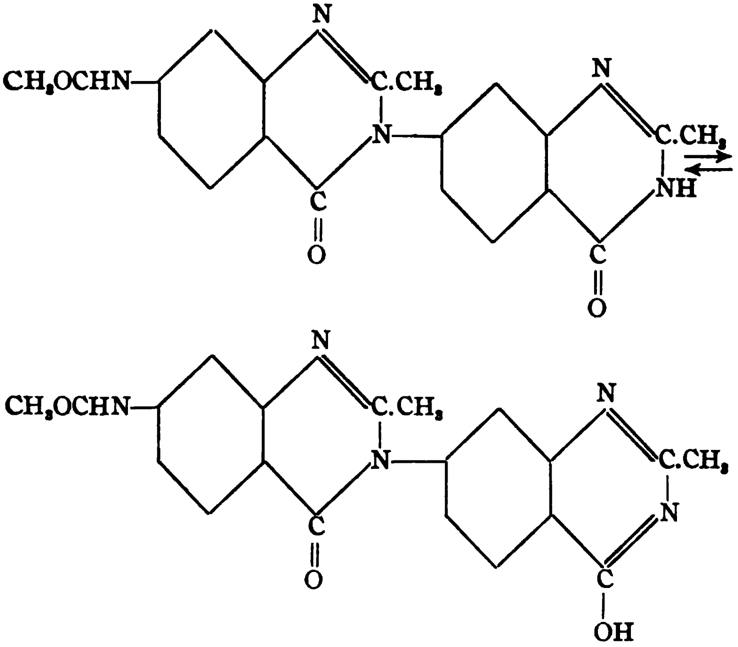
Some of the above brom derivative was boiled with 10 per cent. potassium hydroxide solution for 1 hour, using a reflux condenser. On saturating this solution, after cooling, with carbon dioxide a flocculent, light yellow precipitate resulted. This was filtered off and recrystallized from dilute alcohol. After two treatments with dilute alcohol, light yellow flakes resulted. These gave a strong halogen flame showing that the bromine had not been split off by the above saponification.

0.1111 gram of sample gave 15.8 cc. of nitrogen at 18° and 766 mm.

	Calculated for $C_9H_8ON_3Br$. Per cent.	Found. Per cent.
N	16.53	16.55

This brom-quinazolone, in contrast to the acetamino derivative, is very soluble in hot alcohol and somewhat so in the cold. It also dissolves very readily in warm nitrobenzol and isoamyl alcohol, is soluble in hot water, and insoluble in both hot and cold ether, carbon tetrachloride and chloroform.

7-Acetamino-2-methyl-3-(2-methyl-4-quinazolonyl or 2-methyl-4-oxy-quinazolinyl)-4-quinazolone,



The above compound resulted when a molecular mixture of 7-amino-2-methyl-4-quinazolone and 4-acetamino acetanthranil was fused. The heating was continued to 250° and the product then allowed to cool. As a result a very porous, brittle mass was obtained, the porousness undoubtedly having been caused by the escaping water, as steam, when the condensation took place. A yellow powder resulted upon grinding. This is soluble in hot water, giving a slight green fluorescence, but comes down amorphous on cooling. Solutions of alkalies dissolve it, saturation of these with carbon dioxide causing reprecipitation. Besides this the crude product is insoluble in hot and cold carbon tetrachloride, benzol, ligroin, and ether, and only very slightly soluble in boiling acetone. It dissolves readily in hot nitrobenzol as well as alcohol, but comes down amorphous from both of these solvents. It was finally purified by boneblacking several times with alcohol. Upon concentration of the alcoholic solution to very low bulk, clusters of short, broad, light yellow needles separated out. These are somewhat soluble in cold alcohol and very readily in the warm solution. The mother-liquor showed a greenish fluorescence. The product thus purified begins to darken at 330°, becoming very dark brown and melting at 335° (cor.).

An ultimate analysis gave the following results:

0.1012 gram of sample gave 17.1 cc. of nitrogen at 23.5° and 745 mm.

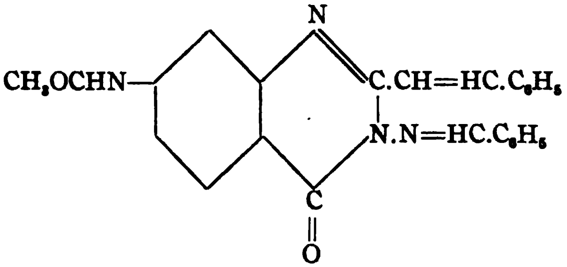
0.1651 gram of sample gave 0.3866 gram of carbon dioxide and 0.0723 gram of water.

	Calculated for $C_{20}H_{17}O_3N_5$. Per cent.	Found. Per cent.
C	64.00	63.86
H	4.53	4.86
N	18.67	18.61

An attempted condensation of 7-acetamino-2-methyl-3-amino-4-quinazolone with diacetosuccinic diethyl ester to form a pyrrole derivative was carried out in the following manner: Molecular proportions of the two were boiled in glacial acetic acid solution for 1 hour, using a reflux condenser, and the excessive acid neutralized with carbonate after cooling. The product thus resulting was proved after purification to be the unchanged quinazolone by a melting point and a nitrogen determination. The above reaction was then repeated with the addition of acetic anhydride. This resulted, however, only in the acetylation of the 3-amino group. A direct fusion of the two constituents also failed to effect the condensation.

IV. Action of Benzaldehyde on Some of the Above Quinazolones.

7-Acetamino-2-styryl-3-benzalamino-4-quinazolone,



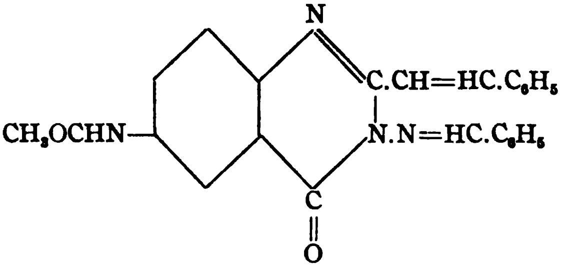
When 7-acetamino-2-methyl-3-amino-4-quinazolone was boiled with an excess of benzaldehyde in a small beaker, it went into solution, water being split off as indicated by cracking. The solution, which is at first amber-colored, becoming darker on concentration, was boiled for 5–10 minutes and then allowed to cool, whereupon clusters of dark yellow needles separated out, the whole mass becoming solid if sufficiently concentrated. By recrystallizing several times from boiling alcohol the product was obtained as light yellow needles, melting at 261° (cor.). In this condensation there are three possibilities, *i. e.*, the benzaldehyde may condense only on the 2-methyl-, only on the 3-amino-, or on both of these groups. A Dumas nitrogen analysis proved that the last-named reaction had taken place, as shown by the following figures:

0.1547 gram of sample gave 19.4 cc. of nitrogen at 24° and 755 mm.

	Calculated for (mono-) $C_{18}H_{16}O_2N_4$. Per cent.	Calculated for (di-) $C_{25}H_{20}O_2N_4$. Per cent.	Found. Per cent.
N	17.5	13.72	13.96

Upon repeating the above reaction the same product was obtained. The purified product gives a deep yellow color with concentrated hydrochloric acid, in which it is only very slightly soluble in the cold. It is insoluble in alkali, hot and cold water, and ether, while it dissolves fairly readily in hot alcohol, acetone, and very readily in hot isoamyl alcohol and nitrobenzol. The alcoholic solution shows a greenish fluorescence.

6-Acetamino-2-styryl-3-benzalamino-4-quinazolone,



When treated in an analogous manner to the above, the 6-acetamino-2-methyl-3-amino-4-quinazolone underwent similar condensation with benzaldehyde. The product is more intensely yellow than its isomer, is more readily soluble in alcohol, and this solution shows a stronger fluorescence.

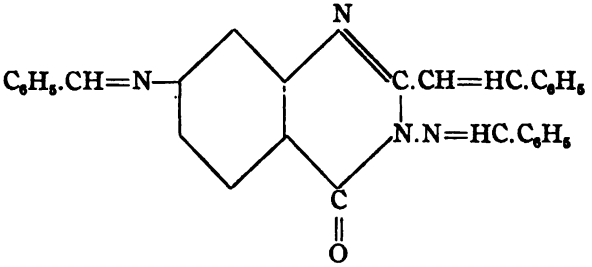
It forms strongly yellow, silky needles, melting at 238–9° (cor.) and is tribo-electric when dry.

A nitrogen determination showed that in this case also a dibenzylidene condensation had taken place.

0.1475 gram of sample gave 17.9 cc. of nitrogen at 22° and 767 mm.

	Calculated for $C_{25}H_{20}O_2N_4$. Per cent.	Found. Per cent.
N	13.72	13.88

3,7-Dibenzalamino-2-styryl-4-quinazolone,



If the 3,7-diamino-2-methyl-4-quinazolone be boiled in the same fashion with benzaldehyde, a condensation likewise takes place, only in this case the main reaction product is a tribenzylidene derivative. After the reaction mixture had cooled, which resulted in the separation of a yellow, granular mass, the latter was stirred up thoroughly with cold alcohol and washed with the same to get rid of the excessive benzaldehyde. It was then boiled up with 50 cc. of 95 per cent. alcohol, in a small flask, with reflux condenser, and this solution filtered hot. By far the larger part remained insoluble. The treatment with boiling alcohol was repeated several times and the resulting light yellow product dried. After grinding to a fine powder the residue was again extracted as above. This treatment removed all traces of benzaldehyde and by-products, leaving the tribenzylidene derivative practically pure. The residue melted at 238° (cor.) and gave the following figures upon complete analysis:

0.1812 gram of sample gave 19.5 cc. of nitrogen at 22° and 766 mm.

0.1577 gram of sample gave 0.4574 gram of carbon dioxide.

0.1508 gram of sample gave 0.0677 gram of water.

	Calculated for $C_{30}H_{22}ON_4$. Per cent.	Found. Per cent.
C	79.30	79.10
H	4.85	4.99
N	12.33	12.29

This tribenzylidene derivative is readily soluble in hot nitrobenzol, isoamyl alcohol, and chloroform; somewhat in hot acetone. It also dissolves in boiling benzol, but is insoluble in both hot and cold alcohol and ether. Concentrated hydrochloric acid turns it a dark yellow but does not effect solution in the cold.

Upon concentrating the above alcoholic extracts, which were colored yellow and showed a slight greenish fluorescence, short, yellow needles separated. These were recrystallized twice from alcohol and analyzed, although the product did not have a sharp melting point, melting from below 185° to 196°.

0.1192 gram of sample gave 16.6 cc. of nitrogen at 23.5° and 751 mm.

	Calculated for $C_{23}H_{18}ON_4$. Per cent.	Found. Per cent.
N	15.3	15.47

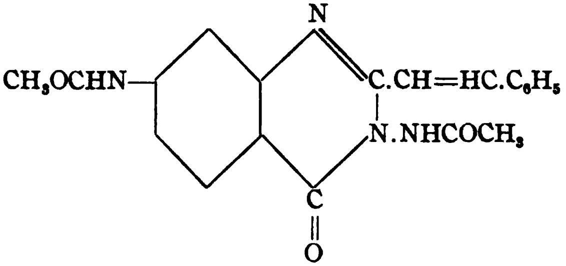
It was thus evident that we were dealing with a mixture of dibenzylidene derivatives. Upon recrystallization a fraction was obtained from the mother-liquor melting quite sharply at 172° (cor.), the other portion melting around 196°. This fraction, of m. p. 172, consisted of dark yellow, glistening plates, and gave the following nitrogen content;

0.1052 gram of sample gave 14.5 cc. of nitrogen at 23.5° and 757 mm.

Found. Per cent.
15.43

These two dibenzylidene condensation products were obtained in far too poor a yield to determine which of the three possible isomers they were.

3,7-Diacetamino-2-styryl-4-quinazolone,



It was next determined to ascertain whether benzaldehyde would act on the N-amino-quinazolone when both the 3- and the 7-amino groups were acetylated. This reagent was therefore made to act on 3,7-diacetamino-2-methyl-4-quinazolone under similar conditions to the above. The quinazolone went into solution rather more slowly than in the other cases. Upon cooling, the reaction product was obtained in the form of greasy nodules. These are very soluble in hot alcohol and somewhat so in the cold. They were therefore recrystallized several times from dilute alcohol. Thus treated the product gave a melting point of 283–4° (cor.), softening a few degrees before melting.

0.1012 gram of sample gave 13.6 cc. of nitrogen at 18° and 762 mm.

	Calculated for $C_{20}H_{18}O_3N_4$. Per cent.	Found. Per cent.
N	15.47	15.56

The analysis thus shows that the condensation took place in this case also. The pure product turns dark yellow and goes into solution when treated with cold, concentrated hydrochloric acid. It is also soluble in hot chloroform, isoamyl and ethyl alcohols, water, cold acetone, and dissolves with great ease in warm nitrobenzol. It is somewhat tribo-electric.

All of the above reactions with benzaldehyde had been carried out with the *bz*-amino-quinazolones containing the N-amino group. We now determined to try the action of this reagent upon a quinazolone in which this group is missing, with the particular object in view of learning how the *bz*-amino group would behave under these circumstances.

7-Amino-2-methyl-4-quinazolone was therefore boiled with benzaldehyde as described above. Rosettes of short, white needles resulted. It required quite a large volume of boiling alcohol to dissolve the product. From this solvent the latter was obtained in short, fine, white, silky needles, the mother liquor being of a very light green color. In this case either a mono- or a di-condensation with benzaldehyde is possible.

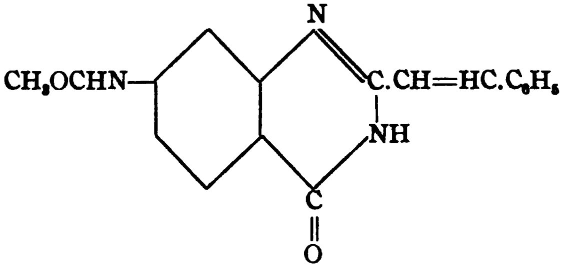
A Dumas nitrogen gave the following results:

0.1224 gram of sample gave 17.6 cc. of nitrogen at 23° and 755 mm.

	Calculated for (mono-) $C_{16}H_{13}ON_3$. Per cent.	Calculated for (di-) $C_{23}H_{17}ON_3$. Per cent.	Found. Per cent.
N	15.97	11.97	16.1

The nitrogen per cent. shows that a mono-benzylidene condensation product had been obtained. The pure product gave a melting point of 324° (cor.). It gives a strong yellow-orange color with concentrated hydrochloric acid, is readily soluble in hot nitrobenzol and isoamyl alcohol, soluble in boiling acetone, while it does not dissolve in hot or cold ether, chloroform, carbon tetrachloride and benzol. It takes a fairly large volume of 95 per cent. alcohol to dissolve it. When boiled with a 10 per cent. solution of potassium hydroxide the benzylidene group is slowly split off, giving back the original quinazolone; after one hour's boiling with alkali, however, the greater part of the unchanged product separated out.

7-Acetamino-2-styryl-4-quinazolone,



To determine with which of the two groups in question the benzaldehyde had condensed, in the previous reaction, 7-acetamino-2-methyl-4-quinazolone was boiled in the usual manner with this reagent. A condensation with the 2-methyl group was thus readily effected. A solid mass of short, whitish, needles resulted from the reaction mixture. The product, recrystallized from alcohol, gave short, white needles melting at 323–4° (cor.). To assure ourselves in the light of what followed, that the reaction would again take place, we repeated the above condensation. The two products obtained are identical and gave the following nitrogen contents:

0.1013 gram of sample gave 12.2 cc. of nitrogen at 22.5° and 762 mm.

0.1116 gram of sample gave 13.9 cc. of nitrogen at 25° and 762 mm.

	Calculated for $C_{18}H_{15}O_2N_3$. Per cent.	Found. Per cent.	Found. Per cent.
N	13.77	13.65	13.94

The pure product upon treatment with concentrated hydrochloric acid becomes intensely yellow at first, then a light cream color. It only dissolves slowly in this acid upon boiling, is practically insoluble in boiling water and ether, while it dissolves readily in boiling acetone, warm nitrobenzol, ethyl- and isoamyl alcohols.

Since our supply of the first monobenzylidene condensation product, namely the one with the free amino-quinazolone, had become exhausted, we again treated 7-amino-2-methyl-4-quinazolone with benzaldehyde. The product resulting this time was neither a mono- nor a di-benzylidene condensation product, nor have we been able since to again obtain the mono-compound with this quinazolone. What is more surprising is the fact that these new products proved in at least two cases in which they were carefully purified by recrystallizing several times from alcohol, to be identical. Thus one, where the quinazolone had been boiled for ten minutes with benzaldehyde, gave a melting point of 324–5° (cor.). Another, where the boiling had been continued for half an hour with a large excess of the aldehyde to effect a dibenzylidene condensation if possible, melted at 325° (cor.). A mixture of the two showed no depression of the melting point, whereas, if mixed with the original mono-product, which melted at 324° (cor.), a depression of 17° resulted. The following results for nitrogen have been obtained in three separate cases:

I. 0.112 gram of sample gave 13.7 cc. of nitrogen at 22° and 761 mm.

II. 0.1116 gram of sample gave 13.9 cc. of nitrogen at 25° and 762 mm.

III. 0.1018 gram of sample gave 12.3 cc. of nitrogen at 22.5° and 763 mm.

	I. Found. Per cent.	II. Found. Per cent.	III. Found. Per cent.
N	13.88	13.94	13.72

The second and third products gave the following values for carbon and hydrogen:

II. 0.1342 gram of sample gave 0.3384 gram of carbon dioxide and 0.0650 gram of water.

III. 0.1519 gram of sample gave 0.3837 gram of carbon dioxide and 0.0671 gram of water.

	II. Found. Per cent.	III. Found. Per cent.
C	68.77	68.89
H	5.38	4.91

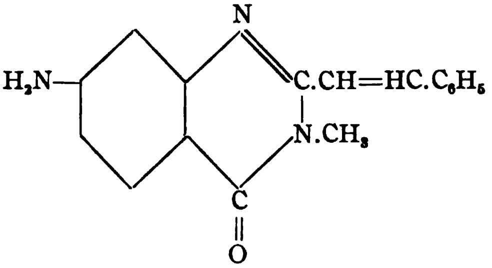
This product is insoluble in hot and cold ether, chloroform, carbon tetrachloride, and benzol. It dissolves in boiling acetone, alcohol, nitrobenzol, and isoamyl alcohol. With concentrated hydrochloric acid it turns at first a strong yellow, then decolorizes. Treated with acetic anhydride an acetyl derivative, which can be obtained in pearly white plates from alcohol, results. This melted at 274–6° (cor.) and gave the following nitrogen content:

0.1011 gram of sample gave 11 cc. of nitrogen at 18.5° and 762 mm.

	Found. Per cent.
N	12.57

The analytical data do not throw any light upon the nature of the condensation of benzaldehyde with 7-amino-2-methyl-4-quinazolone and we are therefore unable to explain this reaction.

7-Amino-2-styryl-3-methyl-4-quinazolone,



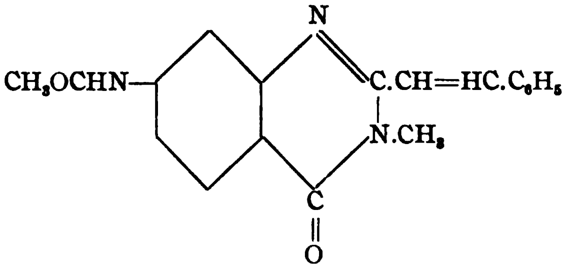
As the above attempts had failed to show whether the *bz*-amino group would react with benzaldehyde in the absence of the N-amino group, 7-amino-2,3-dimethyl-4-quinazolone was next treated with the aldehyde. In this case a definite monobenzylidene product was obtained. The yellow nodules first resulting were recrystallized several times from dilute alcohol, from which solvent, branched prisms, of a strong yellow color, melting at 229.5–230° (cor.), were precipitated. The mother-liquor showed a slight greenish fluorescence.

A Dumas nitrogen determination gave rise to the following figures:

0.102 gram of sample gave 13.6 cc. of nitrogen at 20° and 763 mm.

	Calculated for $C_{17}H_{15}ON_3$. Per cent.	Found. Per cent.
N	15.16	15.31

7-Acetamino-2-styryl-3-methyl-4-quinazolone,



When the above condensation product was boiled with acetic anhydride it went into solution and, upon cooling, light yellow needles separated out. These were recrystallized several times from alcohol, melting, when thus purified, at 272° (cor.). It is thus evident that we were not dealing with the unchanged compound. A nitrogen determination confirmed the fact that the product had been converted into a monoacetyl derivative, and that therefore the condensation with benzaldehyde had resulted in the formation of 7-amino-2-styryl-3-methyl-4-quinazolone since, as mentioned in the introduction, the N-methyl group will not react with this reagent and since the 2-methyl has been shown to do so readily.

0.1112 gram of sample gave 12.9 cc. of nitrogen at 20° and 763 mm.

	Calculated for $C_{19}H_{17}O_2N_3$. Per cent.	Found. Per cent.
N	13.17	13.32

To prove beyond any possibility of a doubt that the last-named product is not a benzalamino derivative, 7-acetamino-2,3-dimethyl-4-quinazolone was treated in the usual manner with benzaldehyde. From this reaction mixture a product melting likewise at 272° (cor.) was obtained. A mixture of this with the acetyl derivative, above mentioned, showed no depression of the melting point whatsoever. The products are therefore identical.

These reactions indicate that the *bz*-amino group does not react as readily with benzaldehyde as do the 2-methyl and the 3-amino groups.

RESUME.

(1) 2,4- and 2,5-diacetaminobenzoic acids when boiled with acetic anhydride are readily converted into 4- and 5-acetamino acetanthranil, respectively.

(2) These anthranils when treated with primary amines yield substituted *bz*-acetamino-quinazolones, amides being the intermediate products of the reaction.

(3) Those quinazolones having a hydrogen in position 3 are capable of acting both in the enolic and ketonic condition, the keto group being rather inactive, however.

(4) In the condensation with hydrazine hydrate a quinazolone having the N-amino group results.

(5) This N-amino group is capable of acetylation, yielding a monoacetyl derivative. It will not, however, condense with diacetosuccinic diethyl ester to form a pyrrole derivative.

(6) The *bz*-amino group is capable of diazotization and can either be replaced by the hydroxy group or yield dyes, depending upon subsequent treatment.

(7) Fuming nitric acid yields a dinitro derivative with 7-acetamino-2-methyl-4-quinazolone.

(8) By action of bromine upon the same quinazolone a monobrom substitution product results.

(9) Monochloracetic ester will not condense with the amino group in the case of 7-amino-2-methyl-4-quinazolone.

(10) By treating 4-acetamino acetanthranil with 7-amino-2-methyl-4-quinazolone, a quinazolone derivative of 7-acetamino-2-methyl-4-quinazolone is obtained.

(11) Benzaldehyde condenses readily with the 2-methyl and the N-amino, but not readily with the *bz*-amino group.

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BIOGRAPHICAL.

Carl Gustave Amend was born in New York City, on January 31, 1887. He entered the School of Chemistry of Columbia University in the Fall of 1904, receiving the degree of B.S. in the Spring of 1908. During the next two years he studied for the degree of Doctor of Philosophy, doing research work in organic chemistry and receiving the degree of Master of Arts in 1909.